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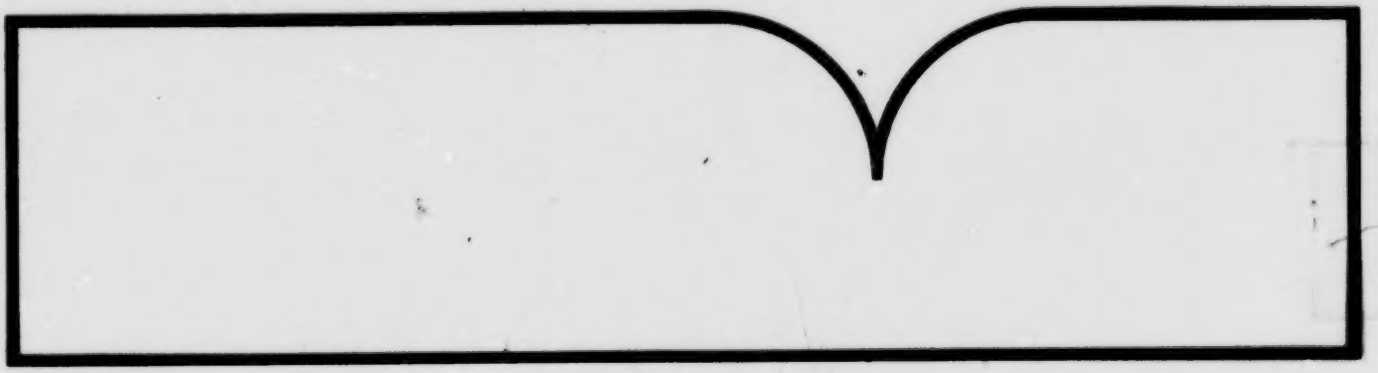

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Health Effects of Fossil-Fuel Combustion Products

Needed Research

Committee on Research Needs on the
Health Effects of Fossil-Fuel Combustion Products

Division of Medical Sciences

Assembly of Life Sciences

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HEALTH EFFECTS OF FOSSIL-FUEL COMBUSTION PRODUCTS: NEEDED RESEARCH

Committee on Research Needs on the Health Effects
of Fossil-Fuel Combustion Products
Division of Medical Sciences
Assembly of Life Sciences
National Research Council

NATIONAL ACADEMY OF SCIENCES
Washington, D.C.
1980

NOTICE

The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the Councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

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INTRODUCTION

This report is intended to assist researchers in providing information that would be useful to regulatory agencies concerned with the protection of workers and the general public from adverse health effects arising from the use of fossil fuels. It examines the research needed to expand and clarify our understanding of the products of fossil-fuel combustion, chiefly that taking place in stationary sources of power.

Several specific objectives guided the study on which this report is based:

- To identify the pollutants potentially hazardous to man that are released into the environment in the course of the combustion of fossil fuels. The hazards of principal concern are those which could cause deleterious, long-term somatic and genetic effects.

- To specify the nature of the research needed to determine the health effects of these pollutants on the general population. Special attention was paid to the interaction of pollutants; the meteorologic and climatic factors that affect the transport, diffusion, and transformation of pollutants; the effects of concentrations of aerosol, particulate, and thermal loads on biologic systems; and the susceptibility of some portions of the population to the effects of pollutants on the skin and cardiovascular, pulmonary, and urinary systems.

- To evaluate the methods of the proposed research, including analytic and interpretation techniques.

- To identify fields in which the available scientific information is inadequate for regulatory decision-making and to recommend a research program to meet those deficiencies.

- To provide a logical framework within which the necessary information can be developed (the proposed program is presented in terms of subject, methods, and priorities).

The study did not address the subject of regulatory decisions, but was limited to the scientific bases on which such decisions can be made.

The discussion of prospective research in this report is categorized by general approach: epidemiology, controlled human-exposure studies, studies on experimental animals, studies of mutagenesis caused by fossil-fuel combustion products, trace-element studies,

methods and problems of analyzing and monitoring pollutant concentrations, and problems related to atmospheric transformation and transport of pollutants. This form of presentation, although it necessitates some overlap of materials among sections, should be useful to those engaged in particular lines of research. However, readers are urged to read the entire report before concentrating on the portions that fall within their spheres of personal interest.

I

SUMMARY AND RECOMMENDATIONS

SUMMARY

Fossil-fuel combustion products that can affect man's health include sulfur compounds (especially sulfur dioxide, sulfuric acid, and sulfates), nitrogen compounds (especially nitrogen dioxide), particles (consisting of carbon, trace elements, and the products of the transformation of gas to aerosol), carbon monoxide, and hydrocarbons and other organic matter. Photochemical oxidants, not directly emitted by combustion, are formed when nitrogen oxides and hydrocarbons react in the atmosphere. Other sulfur and nitrogen compounds--such as sulfites, bisulfites, bisulfates, sulfonates, nitrites, and nitrates--may also affect man's health, but the evidence of adverse effects is scanty.

One can determine how products affect human health by conducting epidemiologic investigations or by carrying out experiments on animals and, where possible, humans. Laboratory investigations on simpler systems, such as isolated cells and enzymes, can provide information about the underlying mechanisms. Each of these research methods provides valuable information, but none, by itself, provides all the information needed. Evidence from all approaches should be integrated to permit sound conclusions to be drawn.

A central interest of research workers investigating the biologic effects of air pollutants is the development of dose-response relationships, in which the magnitude of an effect is related to the amount or concentration of the pollutant in question. To do this, one needs to know the ambient concentrations of the pollutants in the air being breathed, the exposures of the subjects being studied, the doses produced by these exposures, and the biologic responses to these doses. There are difficulties in each of these stages. Problems are encountered in measuring pollutants of interest--even sulfur dioxide, the most frequently measured gaseous pollutant. Better and more widely known are difficulties in measuring particles and determining their chemical characteristics and in measuring nitrogen dioxide, oxidants, and relevant sulfates and nitrates. The difficulties in estimating exposure in epidemiologic studies are obvious: they are related to measurement of outdoor ambient concentrations at one or a few sampling stations, whereas people live at a distance from the station(s), work elsewhere, spend most of their time indoors, and vary widely in their physical activity, breathing patterns, etc. These exposure variations have usually been ignored and have seldom been addressed in any systematic way. For over a decade, it has been recommended that personal monitoring be developed and used to overcome some of these difficulties, but so far

only a few studies have provided any dose-response estimates based on personal monitoring.

Experiments in which humans and other animals are exposed to pollutants at carefully specified concentrations entail much smaller problems of estimating exposure than epidemiologic investigations, but there is still a considerable potential for error. Careful monitoring is essential to ensure that concentrations of pollutants delivered are those which were intended and, in chamber studies, that there has been no unintentional generation of pollutants.

Experimental studies in man have been limited generally to short exposures and to the highest concentrations that are expected to be safe. Exposures are often restricted to young, healthy adults, so the elderly, children, and patients with heart and lung disease (particularly asthma), who may be unusually sensitive to pollutants and therefore most likely to respond, are generally not evaluated. Experiments aimed at measuring the effect of frequent exposures or of exposure prolonged for a few days or the development of chronic disease, including cancer, are difficult to undertake, for ethical reasons. These effects must be studied either by experiments in appropriate animals or by epidemiologic observation. Often, to ensure that a particular effect is produced, animals are exposed to concentrations far in excess of those normally encountered in the ambient air. Thus, there are not only difficulties and uncertainties in extrapolating animal findings to man, but also problems of extrapolating from high to low doses. There has been increasing recognition in recent years of the need for animal experiments in realistic concentrations, that is, concentrations within the range that might be encountered by man.

A serious problem is the multifactorial influence of most biologic indexes used to measure effects. Several factors--such as age, smoking, occupational exposures, and social circumstances--can confound any relationships between pollution and, for example, respiratory disease. These factors should be carefully and adequately evaluated, if the incorrect conclusion that a given effect is due to ambient-air quality is to be avoided. The importance of correct statistical design and analysis of relationships in epidemiologic studies cannot be too strongly emphasized. Somewhat related to this problem of confounding is the problem of determining the degree of interaction of one pollutant with another and of pollution in general with meteorologic and health characteristics.

It is important to evaluate the results of pollution control measures. This type of evaluation can be conducted on the basis of health alone. For example, we may pose such questions as: "What has been the effect of the institution of Britain's Clean Air Act on the health of the people living in London, other cities, and different regions of the country?" "What has been the effect on New York City

death rates of the remarkable decline in sulfur dioxide that has occurred since the institution of the sulfur dioxide standard?" One might use measures of mortality from all causes or from bronchitis or respiratory cancer as appropriate health indexes.

The belief that polluted air is carcinogenic and mutagenic is widespread, and ignorance breeds fear. An increasing number of chemicals are being discharged into the air we breathe, and the discharge is bound to accelerate, particularly with the expected increase in coal use. Thus, although the available evidence does not suggest that ambient-air quality poses a serious threat, there is sound basis for concern, and vigilance is essential.

Knowledge about trace elements is particularly deficient. More needs to be known about the concentrations of trace elements in fossil fuels and in their combustion products, about their chemical states, and about the changes that they undergo after they are discharged. Epidemiologic, human, and experimental animal studies are needed to define the toxic and carcinogenic potential of trace elements.

RECOMMENDATIONS

EPIDEMIOLOGY

- Methods for measuring pollutants in the ambient air must be developed. Much research has been invalidated by the use of faulty methods of measurement. Better methods need to be developed, for example, for various sulfate species, for sulfuric and nitric acids, and for the more complex nitrogen compounds.

- Research should be directed toward better identification of particles in air and toward determination of their physical and chemical properties. Frequency distributions of particle sizes in different places should be established, with a view to selecting the best sites for dichotomous samples.

- Observations should be made on sulfur compounds other than sulfur dioxide in the ambient air that are of possible significance to health. Sulfites, organic sulfur compounds, and sulfonates should be measured.

- Better information is needed on the ambient concentrations of polyaromatic hydrocarbons other than benzopyrene and of other organics, including nitrosamines.

- Relationships of short-term to longer-term concentrations of various pollutants should be studied in different places. In addition, the relationship of 24-h concentrations to those over

shorter averaging periods needs to be better documented. In particular, 1- and 3-h concentrations should be studied and possibly also shorter peak concentrations of 15 min or less.

- A great deal of work needs to be directed toward better estimation of exposure. Estimates of exposure, based on time and motion study and fixed-site samples, need to be checked against results obtained from personal monitoring. Much more attention needs to be given to indoor pollutant exposures. Pollutants should be measured in the home, in the office, and in the workplace.

- The better estimates of exposure so derived need to be related to indexes of biologic effect. Death rates, illness rates, diary estimates of states of health and well-being, telephone interviews and personal visits that incorporate standard questions, and, wherever possible, simple tests of lung function or other functional capacity should be used. The possibility of making observations regularly on stable, accessible, and relatively stationary groups of people (such as schoolchildren, occupational groups, long-term hospital patients, and the institutionalized elderly) who may be naturally exposed to polluting materials should be exploited.

- The effects of changes in pollution, particularly improvement in disease mortality or morbidity in places where pollution has been reduced, should be studied.

- Knowledge of dose-response relationships must be improved, particularly for pollutant concentrations around the ambient-air quality standards (where there are standards) or for critical concentrations at which effects are believed to be produced (where there are no standards). Short-term relationships are more likely to be successfully established than longer-term relationships, but attempts should be made to relate appropriate health indexes (annual mortality and morbidity, symptom prevalence, and respiratory and other function) to these longer-term pollutant estimates.

- Attempts should be made to explore interactions of pollutants. Apart from interaction of one pollutant with another, interactions of pollutants with climate, weather, temperature, and humidity also need to be investigated.

- Studies relating development of cancer to lifetime exposure to various pollutants--particularly polyaromatic hydrocarbons, but also sulfur dioxide and other commonly measured pollutants--are increasingly necessary. These should be conducted both in the workplace, especially where there is a possibility (however remote) of exposure to carcinogenic coal combustion products, and in the general community in the vicinity of coal-burning plants.

- Much more attention should be paid to the statistical aspects of the design of environmental studies and the analysis of their results, especially in the case of costly long-term studies. Encouragement of research in this field should lead to advances comparable with, e.g., those made recently in the design of clinical trials.

• Epidemiologic studies on the risk of mutagenesis and teratogenesis from exposure to pollutants are needed. Studies of abortions, congenital malformations, and chromosomal abnormalities in appropriate communities are most likely to be informative.

EXPERIMENTS ON HUMAN SUBJECTS

• Controlled studies are needed on the effects of human exposure to fossil-fuel combustion products at concentrations around the current national air-quality standards or, for pollutants for which there are no such standards, at concentrations around those at which effects have been suggested. Such exposures are inevitably limited to a few hours. Ethical considerations are of great importance in designing human experiments. Any resulting effects must be completely reversible, and there should be no long-term sequelae. Studies should be conducted on healthy subjects and on persons with mild respiratory or cardiovascular disease, which may increase susceptibility to the effects of pollution. Asthmatic persons appear to be more vulnerable to air pollution than any other people and so may constitute the most sensitive indicators of alterations produced by pollutants. Recently developed tests of bronchial reactivity may provide a safe way of evaluating exposures to potentially hazardous substances. Further work along these lines is needed.

• Exposures to combinations of pollutants at "subthreshold" concentrations should be carried out to determine whether such combinations can cause effects greater than those caused by exposure to the pollutants separately. In all these experiments, it is important to maintain complete control of the environmental conditions. Not only must the concentrations of the substances being investigated be adequately monitored, but no unintentional generation of pollution should occur and humidity and temperature should be adequately controlled. Apart from healthy persons and those in various disease categories, studies need to be carried out on various age groups--children, adults, the elderly--especially when they have been naturally exposed to polluted environments. The desirability of experimental exposure of such groups must be balanced against the ethical constraints associated with experiments that use vulnerable populations, even if low doses of pollutants are used.

• The effects of prolonged exposure to pollutants at low concentrations need study. We need to know more not only about the effects of exposure to a single pollutant on successive days, but about the effects of exposure to a given pollutant on one day followed by exposure to another pollutant on the next day.

• The possibility of a lag between exposure and biologic effect should be investigated in the laboratory.

STUDIES ON EXPERIMENTAL ANIMALS

- Appropriate species, up to and including subhuman primates, should be exposed for short and long periods to fossil-fuel combustion products at low concentrations, and the exposures should be monitored with sensitive indexes of toxic response. Short-term exposures will usually be limited to about 4 h; long-term exposures should include continuous exposure for 24 h or more and exposures repeated over days, weeks, or months. The importance of such intermittent exposures is that they allow for recovery. Long-term changes that result from single short exposures should be determined. Furthermore, the long-term chronic implications of early physiologic responses need more study than they have received.

- Experiments should be carried out on appropriate strains of healthy animals. If reasonable animal models of human diseases of interest are available, exposures should be evaluated in such models.

- Innumerable combinations of animals, pollutants, concentrations, durations, and frequencies are possible. Thus, it is essential to make the best use of finite resources (animals, research workers, laboratories) and to use the most efficient experimental designs.

- Fundamental research is needed on deposition and clearance of aerosols, on sites and modes of action of pollutants, on the relationships between respiratory function and morphologic indexes (such as diameter of the conducting airways) or immunologic status, and on the role of pollution in the biochemistry of the lung and other organs.

- Studies of the effects of combinations of pollutants administered at the same time or on different occasions are particularly needed. Synergism between pollutants is of great current interest, and exposure to a combination of pollutants is a better model of the human situation than exposure to a single pollutant.

- Studies of the effects of temperature and relative humidity on aerosol size and, therefore, aerodynamic characteristics are needed.

- The risk of cancer from short-term or long-term exposure to fossil-fuel combustion products at the concentrations likely to be encountered by man needs further assessment.

- There is a great need to improve the statistical procedures used in monitoring pollutants, in determining dose-response relationships, in designing experiments, and in setting standards.

TRACE ELEMENTS

- Trace elements in emissions, ambient air, and the air related to various occupations should be identified, measured, and characterized. Information on secondary pollutant formation, speciation, and vapor- and particulate-phase relationships is especially needed.

- The nature and leachability of the trace elements and metallo-organic substances present in solid and liquid residues--such as retort, quench, and scrubber water, fly ash, and slag--need study.

- Better understanding is needed of the bioconversion and bioaccumulation of trace elements, their incorporation into the food chain, and their persistence in the biosphere. Particular attention needs to be directed to arsenic, chromium, nickel, cadmium, and beryllium, which have been associated with carcinogenicity. The oxidation states of arsenic and chromium are important, because they apparently influence carcinogenic potential.

- Long-term, low-concentration exposures of laboratory animals to trace elements are needed to determine their pathophysiologic and biochemical effects. Gaps in understanding of pulmonary and gastrointestinal absorption, distribution, metabolism, and excretion need to be filled.

- Synergism between trace elements, between trace elements and other pollutants, and between other environmental constituents that are carcinogenic, such as ionizing radiation, are especially needed.

- Human studies are particularly important. Short-term pharmacokinetic studies of trace elements that may pose a low risk of cancer and for which sensitive methods of detection are available--such as lead, cadmium, mercury, and selenium--should be conducted, with appropriate consideration for the safety of the subjects.

- Assays of hair, nails, teeth, fat, blood, and excreta need to be carried out on representative samples of the community and on groups thought to be at risk of exposure to higher concentrations. Epidemiologic studies of populations living in the vicinities of power plants and fuel-production sites could provide much needed information on exposures to trace elements and their accumulation in the body.

TRANSFORMATION AND TRANSPORT OF POLLUTANTS

- Research is needed on the alterations that pollutants undergo after they are emitted. Changes in the physical and chemical

characteristics of aerosols, the development of secondary pollutants, and the dispersion and removal of pollutants from the ambient air all need further study.

ANALYSIS AND MONITORING

- Improved methods for analyzing particle-size distribution are needed.

- Improved methods for analyzing the chemical species in fine aerosols should be developed.

- Concentrations of toxic metals in combustion effluent and in the fine and aerosol fractions should be investigated.

- Analyses should be correlated with concentrations that damage human health.

- Personal monitors that are adequate for the more subtle analysis now thought to be necessary must be developed.

MUTAGENESIS

- More data are needed on specific fossil-fuel combustion products at the specific concentrations that pose a significant carcinogenic threat to exposed populations.

- Experiments designed to evaluate directly an association between air pollutants at ambient concentrations and lung cancer in animals are needed.

- Epidemiologic study of a possible mutagenic effect of ozone is sorely needed.

- Studies on the interaction of ozone and aromatic hydrocarbon carcinogens are necessary.

- The biologic pathway by which ozone is associated with lymphocyte chromosomal abnormalities should be studied.

- Studies of the mutagenicity of photochemical oxidants other than ozone are required.

- The conversion of the nitrogen oxides to other mutagenic agents requires study.

- A study is needed on the extent to which atmospheric nitrogen oxides participate in the formation of N-nitroso carcinogens and the impact of these derivatives on human cancer.

- Evaluation of the suitability of the use of benzene-soluble fractions of polycyclic organic materials and of benzo[a]pyrene as representative indexes of the group of polycyclic organic materials with respect to carcinogenicity requires study.

- Information is needed on the organic chemical constituents of respirable particles.

- The interaction of airborne organic compounds with other atmospheric pollutants must be studied.

- The mutagenic effects of trace elements emitted during fossil-fuel combustion require study.

- Studies should include human epidemiologic evaluation and experimental studies in animals, tissue-culture systems, and *in vitro* systems.

II

EPIDEMIOLOGY

One way of approaching the question of the impact of the environment on health is through epidemiologic studies. Epidemiologists relate exposure to response in definable populations and present their findings in the form of dose-response curves. These provide the essential basis for deciding on permissible ambient concentrations and eventually on standards of acceptable air quality. Many factors other than air pollution can cause responses of interest, and due allowance must be made for these confounding factors, if exaggerated statements about the hazards of air pollution are to be avoided.

Epidemiologists are also interested in seeing how changes in the environment, particularly those brought about the institution of control measures, influence health effects. Thus, monitoring of the environment and surveillance of disease frequency in the community constitute one of their major modes of study.

Epidemiologic studies, clinical exposures of humans, and experiments in other animals complement each other. None of them provides precisely the information one would like to have. Epidemiologic studies use uncertain estimates of exposure. Clinical exposures of humans are limited to short-term changes in response to, at most, three pollutants. Animal experiments, although they provide an opportunity to measure long-term chronic and carcinogenic effects, also encounter difficulties in simulating the ambient air. Evidence from all three types of investigations must be carefully sifted and integrated, if the soundest assessment of all the available evidence is to be made.

Fossil-fuel combustion products emitted into the air include particles, sulfur oxides, nitrogen oxides, hydrocarbons, and carbon monoxide. Photochemical oxidants, which are not emitted directly, are formed when nitrogen oxides and hydrocarbons react in the atmosphere. Many reviews on the effects (including effects on health) of these pollutants have been published during the last 10 yr.[86,88-91,116,117,123] No useful purpose would be served by adding to them or reviewing them in detail here. The reader is referred to the succinct but comprehensive statement by Ferris[39] and the more encyclopedic publications.

KINDS OF EPIDEMIOLOGIC STUDIES NEEDED

EFFECTS OF LOW CONCENTRATIONS

Few persons doubt that most pollutants cause adverse health effects if their concentrations are high enough. The problem is to determine the critical concentrations at which important effects develop. Because the cost of purer air increases steadily as background concentrations are approached, small differences in the estimates of critical concentrations can have large economic implications. It is clearly unsatisfactory, in determining air-quality standards, to have to add large safety factors born of uncertainty in order to protect the public health.

Epidemiologic studies are needed to explore the effects of low concentrations of pollutants on health. Such studies should be directed particularly to concentrations near the national ambient-air quality standards (where such standards exist) or to concentrations previously indicated to be of possible concern (where they do not). Studies should be made on the general population, which comprises mainly healthy persons, and also on susceptible groups, notably persons with cardiovascular and respiratory diseases.

Both short-term changes, such as absenteeism and hospital admissions (usually resulting from exposures of up to 24 h, or at most a day or two), and long-term effects, such as altered morbidity and mortality patterns (usually resulting from cumulative exposures of anywhere from a year to a lifetime), need to be assessed.

Some pollutants resulting from fossil-fuel combustion are already known to pose a risk of cancer. The development of synthetic fuels and the liquefaction and gasification of coal may add to the carcinogenic potential of the air. Introduction of carcinogens into drinking water as a result of these new technologies poses an additional risk of cancer from ingestion, as well as from inhalation. Thus, epidemiologic studies need to be directed toward cancer as one of the significant long-term outcomes. The fact that most carcinogens are also mutagens, coupled with the increasing identification of mutagens and teratogens in the ambient air, suggests that more attention should also be given in epidemiologic studies to effects of teratogenicity and mutagenicity.

EFFECTS OF INTERACTIONS OF POLLUTANTS

Since the classical episodes of pollution damage, it has been widely believed that the effects on human health are largely attributable to the whole pollution complex. Individual pollutants, such as sulfur dioxide, or heterogeneous mixtures, such as total

suspended particulate matter, may have been used in analyzing exposure-effects relationships; but it has always been recognized that these components were indexes of a particular type of pollution (which fortunately were measurable), and were not necessarily the particular substances responsible for the effects. In spite of this, nearly every review of the effects of air pollution has focused on a single component: sulfur oxides (sulfur dioxide, in most of the studies reviewed) or particles (smoke, in England; the wide range of particles collected by a high-volume sampler, in the United States). Several reviews have noted that particles and sulfur oxides should not be considered separately, but then the evidence has been handled as though they could be.

It is important to determine whether specific effects are in fact produced by specific pollutants. If they are, concentrations may be reduced sufficiently to eliminate at least the serious effects. However, if the problem is, as has been thought, mainly one of adverse effects from a combination of pollutants, then preventing the effects of combinations by controlling one of the elements may be adequate to eliminate the effects. Sulfur dioxide and particulate matter provide an illustration. In London, England, in the 1950s, smoke and sulfur dioxide were the two indexes of pollution that were routinely measured. It was not possible, by studying the episodes of pollution or by analyzing daily mortality and morbidity in relation to daily smoke and sulfur dioxide concentrations, to decide which of the two, if either, was responsible for the excess mortality and morbidity that pollution clearly caused. Smoke was undoubtedly the more objectionable from an aesthetic and practical standpoint. It regularly disrupted traffic and sometimes brought the city to a standstill. It was also easier and cheaper to control. Not surprisingly, the focus of the relevant legislation was on smoke. Sulfur dioxide was largely ignored, so its concentration remained relatively high in London for many years after smoke had been impressively reduced. This policy appears to have been effective, as judged by episodic criteria, in reducing the adverse effects of pollution (at least in London) at a fraction of the cost that would have been incurred if control had been directed at sulfur dioxide or both smoke and sulfur dioxide.

A pollutant may be hazardous not for itself but for what it may become. A primary pollutant, such as sulfur dioxide, may be relatively innocuous, but be transformed in the atmosphere as a result of oxidation or other chemical reactions into harmful secondary pollutants. The brunt of the harm may be felt not where the primary pollutant is discharged, but at some distance, possibly many miles away. It has been widely believed for about 10 yr that, although sulfur dioxide is relatively harmless, it is transformed in the atmosphere into sulfuric acid and acid sulfates, which are far more irritating and therefore potentially more hazardous to health.

These pollutants occur in a range of sizes and may remain suspended in the air for a long period. During that time, they may be transported many hundreds of miles, depending on the prevailing wind, before being deposited. Adverse effects of sulfates may be experienced miles from the site of sulfur dioxide formation. The validity of these assumptions needs to be tested. Epidemiologic analyses can relate health effects only to pollutants to which people in the community under study are exposed. Some estimate of the relative toxicity of different pollutants can be made in such studies. Although the sources of primary pollutants may be obvious, the sources of secondary pollutants may be highly problematic.

Epidemiologic studies are needed to explore interactions between pollutants: particles and sulfur dioxide, sulfur dioxide and oxidant, nitrogen oxides (mostly nitrogen dioxide) and various combinations of other particles and gases.

Considerable interest was stimulated a few years ago by reports of synergism between sulfur dioxide and ozone in reducing lung function in humans. It appeared at first that clear evidence of the importance of interaction between these two pollutants had been found. This could have had important implications for areas of the country where ozone concentrations are naturally high. A lower concentration of sulfur dioxide might have had to be recommended there than in places where ozone tends naturally to be lower. Further research has cast doubt on the relationship of interaction between these two gases and lung function. But the extent to which any synergism occurs between these and other pollutants needs to be measured both in the laboratory and in the general community.

Epidemiologic studies are needed to explore relationships between pollutants and meteorologic, climatic, and weather factors. Temperature and humidity in particular are important variables that may influence the effects of exposure to pollutants. The extent to which pollution and temperature interact or produce similar effects that may be confounding needs particularly careful analysis.

Many of the factors discussed later may also interact with pollution to produce effects. In analyzing data, the question can arise as to whether confounding or interaction is the more important. The influence of influenza on daily mortality is an example. In New York City, Buechley and colleagues[20] treated influenza epidemics as a confounding variable and removed the effect before looking at pollution. But if pollution acts to increase the mortality from influenza, then treating influenza purely as a confounding variable will result in an underestimate of the effect of pollution. Smoking, occupational exposures, infections, and social-class characteristics need to be considered from the standpoint of interaction, as well as of confounding.

BENEFITS OF IMPROVED AIR QUALITY

Clean-air policies have resulted in great improvement in ambient-air quality. The effect of reduction in pollutant concentrations on health in different places needs to be assessed. Cost-benefit analyses of air-pollution control have usually been based on anticipated improvement in health or reduction in disease. There have been some remarkably precise estimates of the changes to be expected from unit changes in average concentrations of this or that pollutant. Naturally, such signal benefits of reduction in pollution have caught the public imagination and have impressed legislators. Reductions in pollution that have been achieved in different places enable critical tests of the expected benefits to be made. Epidemiologic studies on trends in various health indexes over the years in different places should be conducted.

It is, of course, possible that the increasing use of high-sulfur fuel will lead to substantial deterioration of air quality in some places. Epidemiologic surveillance is essential, if the health impact of such deterioration is to be adequately measured.

EFFECTS OF EPISODES OF POLLUTION

The classical types of pollution episodes of the 1950s and 1960s are unlikely to recur. But epidemiologists should be alert to exploit the situation if they do recur. This is most likely to prove feasible in cities in which efficient monitoring is already in place. High concentrations of oxidants, including ozone and nitrogen dioxide, may, however, occur in some cities, and these may afford an opportunity for measuring short-term biologic changes. One approach to short-term changes in pollution, including peaks of high pollution, is to study people living in the vicinity of a point source, such as a power station. As ambient concentrations change (depending on emissions, wind speed, and other meteorologic considerations), it should be possible, by monitoring exposures and observing appropriate related health indexes, to obtain better dose-response data than are now available.

IDENTIFICATION, EVALUATION, AND SURVEILLANCE OF NEW POLLUTANTS

A great deal of work is needed to evaluate effects of chemicals that have been present in polluted air for years, but epidemiologists also need to be alert to the possible hazards of new toxic substances. Environmental chemists and animal toxicologists can best advise on potential impending hazards, and close communication between these disciplines is clearly desirable.

DETAILED CONSIDERATIONS

EFFECTS OF LOW POLLUTANT CONCENTRATIONS

Measurements of Pollution

What pollutants should be measured? What analytic methods should be used? Over what period should concentrations be averaged? Where should samples be taken, and how many sites are needed in order to obtain valid estimates of personal exposure? These important questions are often overlooked in epidemiologic studies. Some epidemiologists may consider these questions to be of more concern to engineers and hygienists. But it must strongly stated that measurement of the environment and estimation of personal exposure is as much the concern of the epidemiologic study as measurement of any biologic changes that such exposures may provoke. More studies have been invalidated by poor estimates of exposure than by poor measurements of response.

There are practical limitations to the pollutants that can be studied by epidemiologic means. Of the sulfur compounds, sulfur dioxide can be routinely monitored in emissions and in the ambient air. High temperature was recently shown to invalidate much sulfur dioxide measurement by the West-Gaeke method,[18] and appropriate precautions to avoid this problem need to be incorporated into collectors. Hydrocarbon interference with measurement of sulfur dioxide from continuous monitors may also be a problem. These examples are cited to show that even methods that have been used for years to measure pollutants may pose problems. Acid sulfate aerosols (sulfuric acid, ammonium sulfate, and ammonium acid sulfate) can be differentiated by size and chemical species. These can be included in special surveys, but are not yet applicable to routine monitoring. The use of total water-soluble suspended sulfate extracted from high-volume filters is perhaps the most practicable method for community surveys, but even it is not adequate. More sophisticated research methods need to be developed for routine field use.

Epidemiologic observations on other sulfur compounds (e.g., sulfites and sulfonates) have been scanty or nonexistent. Efforts should be directed to determine whether such compounds remain in the ambient air long enough and in sufficient concentrations to pose hazards.

The term "total suspended particles" (TSP) is generally agreed to be vague. Much more attention must be directed at identifying the particles and determining their physical and chemical properties.

Special attention needs to be given to size distribution, because deposition in the respiratory tract and the chemical constituents of the particle depend on size. A recent recommendation of the Environmental Protection Agency is that collection of airborne particles be carried out using two sizing levels, one at an aerodynamic diameter of 15 μm, and the second at 2.5 μm. There are sound theoretical and practical reasons for this recommendation.[114] The fraction of particles under 15 μm includes the vast majority of particles that penetrate into the tracheobronchial tree. The fraction under 2.5 μm consists of particles that penetrate deeply into the alveoli. Thus, such sizing would permit differentiation of alveolar and tracheobronchial deposition. Particles should continue to be collected by standard high-volume samplers, to ensure continuity with previous measurements. There is some uncertainty about the lower size level. In industry, for example, the cut is made at 3.5 μm. Whether it makes much difference to use 2.5, 3.5, or even 5 μm as the lower cut point needs investigation. Special studies of the complete range of particle size should be made in different places, so that the best size levels can be specified with greater certainty.

The transport and transformation of the urban gas-aerosol complex have been investigated in a number of multidisciplinary studies, which have used advanced techniques to measure and categorize sulfur oxides and particles. The lack of an epidemiologic component in these studies, which will be difficult to replicate, is regrettable. The need for better coordination of environmental with biologic research is obvious.

Earlier epidemiologic studies of the effects of nitrogen dioxide were invalidated because the measurement methods were unsatisfactory. Adequate methods are now available. Nitrate and ammonium ions have been included in the data provided by the National Air Surveillance Networks for many years. The value of these concentrations as a basis for determining past exposures is questionable, but warrants exploration. Analytic methods for nitric acid and the more complex nitrogen compounds need improvement before they can be included in epidemiologic surveys.

Reasonably satisfactory methods are available for measuring carbon monoxide, oxidants, and peroxyacetyl nitrate (PAN) in epidemiologic studies. However, there is some controversy concerning appropriate siting of carbon monoxide monitors in relation to traffic flow and pedestrian exposure.

The potential conservation of energy from an increased use of diesel-powered engines indicates the need for increased research into the impact of diesel emission on health. Particles, nitrogen dioxide, and hydrocarbons are the pollutants whose concentrations are most likely to increase with increasing diesel use. Thus, this prospect is an additional stimulus for making adequate measurements

of these pollutants. The use of shale oil and of synthetic fuels from liquefaction and gasification of coal may increase environmental concentrations of polyaromatic hydrocarbons. Methods for identifying and measuring such hydrocarbons that would be suitable for epidemiologic studies are needed.

It is obvious that measurements of many pollutants of potential interest will not be included in epidemiologic surveys. Special environmental studies are in order, to see how well (if at all) the concentrations of unmeasured pollutants can be predicted from those of pollutants that are included.

The importance of the time over which measurements of pollutants are averaged is often overlooked. Most short-term epidemiologic studies have been based on 24-h average pollutant concentrations. Although such values reflect shorter exposures (1 h, 15 min, etc.), to some extent they leave one in doubt about the pattern of these exposures within the 24 h. The pattern could be important in considering some biologic responses (such as asthmatic attacks) that could be precipitated by a transient high concentration. Longer-term studies have most often been concerned with the average annual concentration of all the 24-h values. The relationship of the frequency distribution of the 24-h concentrations to the average annual concentration needs to be considered. The shorter the averaging period, the more important it is that personal exposure be determined by personal monitoring, because short exposures are likely to vary more from place to place than longer ones.

National sampling networks are not planned primarily for epidemiologic purposes. The siting of sampling stations is usually dictated by convenience and by the need to monitor more important sources of pollution. By careful selection of available sites, it should be possible to obtain a useful indication of population exposure. But, in most places, additional sampling will have to be done, if pollutant concentrations are to be even estimated. This is particularly necessary in rural areas. Research is needed on the number and distribution of sampling stations that are required to provide valid estimates of individual exposure.

Estimating Exposure

The difficulties of estimating exposures to air pollutants are now well recognized. For example, people may live at some distance from the sampling station and thus not be exposed to pollutants at the concentrations measured there; estimates of concentrations in the vicinity of the home may be inaccurate. Most people work away from their homes. They travel between their homes and their places of work and move about elsewhere during the day. Furthermore, most people spend a relatively small fraction of the day out of doors, where most samples are taken.

The concentrations of most pollutants indoors and outdoors have been shown to differ. Some pollutants are more concentrated indoors, others less; there is no consistent trend. Indoor concentrations depend on indoor generation, absorption, ventilation, etc. Particle concentrations vary greatly and depend in part on whether members of the household smoke. In smoking households, particulate and carbon monoxide concentrations may be higher indoors than outdoors. Nitrogen dioxide and carbon monoxide may be higher or lower indoors, depending on whether gas or electricity is used for cooking. Sulfur dioxide is usually lower indoors. Unvented heaters and fireplaces may also affect the particulate and carbon monoxide concentrations. There is no simple formula that will allow prediction of the indoor-outdoor difference for any pollutant, depending as it does on a number of circumstances. The resulting uncertainty decreases the accuracy of assessment of a given person's exposure.

Personal monitoring is an obvious aid to the estimation of exposure. It has been recommended for years, but few epidemiologic studies have made much use of it. This deficiency should be remedied. Personal monitors are available for a number of pollutants (e.g., particles, sulfur dioxide, acid sulfates, and nitrogen dioxide), and further development of personal monitoring for epidemiologic studies is needed. But considerable research to assess currently available estimates of exposure also needs to be carried out. In particular, estimates of individual exposures based on fixed-site sampling combined with time-and-motion studies should be compared with measurements from personal monitoring.

Estimating a person's exposure over a day or two raises serious difficulties. These difficulties are compounded when estimates for the last 10 or 20 yr or for a person's lifetime are attempted. In such a case, one has to allow for changes in residence, changes in pollution, and lack of adequate measurements of pollutants in the past. Although careful residential and occupational histories can provide some information, the estimates of past exposure are inevitably crude. Biologic estimation of exposure can be useful; examples are the measurement of heavy metals in hair and nails, of various chemicals in tissues or tissue fluids, of carboxyhemoglobin in blood, and of carbon monoxide in expired air.

Measurements of Response

The biologic indexes that are available for measuring effects of air pollution on people have been detailed on many occasions (e.g., Comar and Nelson[26]). They range from death, severe disability, and severe illness at one extreme, through milder illnesses, respiratory and other symptoms, and lung and other functional changes, to unnoticed physiologic or psychologic changes and silent

accumulation of chemicals in the body at the other extreme. Some such data are collected routinely. Numbers of deaths, including daily numbers, are available for some cities from the National Center for Health Statistics; information on morbidity is available for insured populations and can also be obtained, though less satisfactorily, from hospital admission records. Deaths from all causes or from specific diseases and incidences of illnesses can be used. When confirmed by a valid death certificate, the fact of death is particularly useful. Recording of specific causes of death leads to a number of problems. Some are related to diagnosis; they include criteria for diagnosis, fashions in certification, and observer variation and error. Others reflect the difficulty of identifying potentially lethal conditions on a death certificate. Finally, problems arise because there are competing causes of death. Thus, the number of persons who die of coronary disease in their 50s affects the number who die of cancer or stroke in their 60s or 70s.

The limitations of routinely collected statistics are considerable. Records of occupational exposures are usually inadequate, and records of smoking habits, nonexistent. A special survey is necessary to collect such essential missing information. It is usually possible to define the index of response more precisely than in the case of available data. Attention can be given to a more satisfactory classification of responses by degree of severity. The reproducibility of symptoms, physical signs, special investigations, and functional, biochemical, and psychologic tests can be established.

Because the brunt of air pollution falls on the respiratory system, the focus of interest in most air-pollution studies is on this system. Much effort has been directed by epidemiologists to developing appropriate tests. Respiratory symptoms (cough, sputum, wheezing, and breathlessness) and a history of past chest illness are particularly useful. Symptoms are usually recorded with a standardized questionnaire, which includes information on smoking habits, occupational exposures, and exposures within the home from various sources, especially home heating and cooling. Tests of lung function provide objective evidence of impairment. Impairment of ventilatory lung function as measured by simple spirometry has proved most useful. The forced expiratory volume in 1 s (FEV_1) and the forced vital capacity (FVC) have been most often measured, but other quantities--such as flow rates after various percentages of the vital capacity have been expired--may be measured. Other laboratory tests, such as measurement of airway resistance or of lung compliance, are also valuable, but not for field study. A task group of the American Thoracic Society has presented recommendations for conducting respiratory-disease studies.[38] A well-designed survey that combines recording of respiratory symptoms with objective measurement of lung function provides one of the most useful methods of assessing the health effects of pollutants whose main impact is on the respiratory system.

Other symptoms and tests may be more appropriate for other pollutants. The rate of development and frequency of anginal pain in patients with coronary disease, impairment of fine discrimination, and more serious physiologic disturbances have proved useful for assessing carbon monoxide exposure; eye irritation has been valuable in the case of oxidant exposure. Finally, accumulation in the body of such pollutants as lead, mercury, and cadmium--clearly an index of exposure--is also an effect whose implications need to be assessed by epidemiologic studies.

Comar and Nelson[26] emphasized the importance of including effects related to the financial cost of pollution. They suggested recording working days lost through sickness and premature death and days spent in bed or in the hospital, to which may be added the cost of physicians' care.

Allowance for Confounding Factors

Many factors other than air pollution can influence the development and severity of disease, particularly respiratory disease. Smoking habits, occupational exposures, infection, allergy, heredity, age, sex, and socioeconomic status need to be carefully assessed before any case of respiratory disease is attributed to air pollution. Climate, especially temperature and short-term changes in temperature, may also contribute significantly to disease. Unless these confounding variables are adequately allowed for, some effects will be wrongly attributed to air pollution, and the hazards will be exaggerated.

Analytic Problems

A large body of collected data--health effects, pollution measurements, and other information on individuals and communities--may be studied statistically by various methods. The work of Schimmel *et al.*[106-108] is typical. Lave and Seskin[72] prefaced their study with some remarks on methods; they also commented on the type of data analysis used by others, such as Schimmel *et al.* The EPA reports on its Community Health and Environmental Surveillance System (CHESS) studies, and even more the various critical reanalyses, also contained extended discussion of how, and how not, to design such investigations and analyze their results.

It is likely that not every variable is quite what one would wish. In the CHESS studies, the asthmatic attack was an important health effect, but it turned out to be hard to define in practice. Death is unequivocal, but statements as to cause of death are not always dependable. Weather variables also cause trouble. Surrogates

of various degrees of relevance must often be used, such as socioeconomic status. "Day-of-the-week" effects might be related to the way the data are collected; e.g., the asthmatic-attack data mentioned above were reported in weekly diaries. If such an effect is strong, it might outweigh the effect of environmental variations.

Given the variables, one seeks to express a health effect as a function of all the other variables. If there are very few explanatory variables, one can explore a number of functions, including ones that allow the variables to interact, in order to get a good fit. Scientific understanding can occasionally guide the choice of functions. If variables move together, their effects are confounded, and no amount of computing will unscramble them. In designed experiments, one can prevent this; but in most epidemiologic situations, variables cannot be controlled. When there are many variables (and usually when there are not), it is hard to consider functions that are not linear. Such functions cannot make biologic sense over large ranges of the variables. It is usual to say that a particular variable has a deleterious health effect if the coefficient in the linear function is "significantly different from zero" and has the appropriate sign. Apart from the difficulty of estimating coefficients accurately when the variables move in similar ways, the quoted phrase depends on assumptions that are difficult to check.

Thus, there are many pitfalls in these studies, and it is hard to draw firm conclusions unless the effects are large. Many of the simplifications due to lack of interactions that one sees in other applications of statistics are strikingly absent here--synergism seems almost to be the key to these problems. Surprisingly few statisticians have been involved in this kind of research, as opposed to the clinical trials and controlled animal studies in which much progress has recently been made. An effort in this direction might lead to some similar advances for uncontrolled studies.

It is convenient to collect here the other statistical contributions that it is hoped can be made in this field. In the setting of pollution concentrations to ensure that environmental quality satisfies the law, many statistical problems arise. These may be more subtle than the cost-benefit approach of Lave and Seskin.[72] They usually involve not only the relation between exposure and health effects, but also the statistical variability in exposures. Different methods will be necessary for substances that act very differently, e.g., the immediate response to a peak in ozone concentration compared with the apparently cumulative effect of smoking. Much effort has been made in the study of carcinogenesis to model the process so that the problems of low-dose extrapolation and computation of risk might be tackled. Although this work has not been entirely convincing, most current discussion of allowable pollutant concentrations is in these terms. The monitoring of

pollutants is a process of sampling in space and time. Far too little effort has been devoted to it.

EFFECTS OF INTERACTIONS OF POLLUTANTS

The effects of interactions between pollutants and between pollutants and other factors must usually be studied by analysis of collected data. It is obvious that such analysis is possible only for variables that have been included in the initial survey or on which information is available from other sources. Important variables have often been lacking or inadequately specified. Every effort must be made in future research to collect information on all factors that are known or believed to influence the health indexes under consideration.

The effects of specific interactions can sometimes be tested. It may be possible to identify places high in one pollutant, such as sulfur dioxide, but low in others. Comparison of such places with others where, for example, sulfur dioxide and particles vary concomitantly may throw light on sulfur dioxide-particle interaction. Similarly, it might be possible to identify a polluted city where temperature is reasonably uniform throughout the year. Comparison of such a city with London or New York City would be particularly instructive. Instances of reduction in one or several pollutant concentrations through control measures also provide a means of studying interactions between pollutants.

For many years, young children have been used as controls in the study of the effects of cigarette-smoking and occupational exposure. Women, too, were less likely than men to smoke or to work in occupationally polluted jobs. Studies of the effects of general pollution on women and children may be particularly helpful in the assessment of interactions.

EFFECTS OF INSTITUTION OF CONTROL MEASURES

Surprisingly little research has been directed at measuring the health effects of long-term changes in pollution. In Britain, Lawther *et al.*[73] have reported a reduction in the frequency of exacerbations of bronchitis among patients with bronchitis as a result of the reduction in smoke pollution from the high levels of the 1950s. There has also been some decline in the annual mortality from chronic bronchitis and emphysema over the last 20 yr.[36,132] In this country, few observations have been made.

It has been claimed that the reduction in sulfur dioxide concentrations in New York City in recent years has not influenced mortality, but the basis for this claim is debatable; a more convincing demonstration that there has been no effect is needed.

More systematic study of mortality and, if possible, morbidity in areas where pollutants have been reduced would be useful. It should, however, be pointed out that it is difficult to control for other factors that could have influenced mortality. In particular, changes in smoking habits (including the increased use of low-tar, low-nicotine, or low-carbon monoxide cigarettes), changes in patterns of migration, and improved medical care could all result in a reduction in mortality.

The emphatic and often improbably precise predictions that some authorities have made on the expected effects of reducing pollution should be put to the critical test. Longitudinal observations on mortality and the results of prospective studies afford the only means of doing so.

III

EXPERIMENTAL SYSTEMS

CONTROLLED-HUMAN-EXPOSURE STUDIES

Controlled-human-exposure studies are those in which humans are exposed to known pollutants at defined concentrations in situations in which their responses can be accurately measured. In essence, this approach bridges the gap between the laboratory efforts of the animal experimenter and the field work of the epidemiologist. Animal studies are most likely to discover the types of effect and mechanisms of action of pollutants. However, because of differences among species, the quantitative relations to human health are left in doubt. Epidemiologic studies have the advantages that exposures occur "naturally" in the community and that it is possible to study long-term or delayed effects, such as heart disease, cancer, and emphysema. The many possible confounding variables interfere with interpretation of causality and dosage.

Ethical considerations are of great importance in designing human experiments. In general, controlled-exposure studies with human volunteers have been limited to short exposures to defined single pollutants or pollutant mixtures. The pollutant concentrations are kept within the range present in the ambient atmosphere. Furthermore, the expected acute effects must be reversible and measurable without significant risk to the subject.

Proposed studies involving human experimentation are intensely scrutinized by institutional review boards. Unfortunately, such boards sometimes appear to have acted in the spirit more of preventing litigation than of protecting subjects and facilitating research. The constraints imposed by overzealous review boards can stifle safe and beneficial research inappropriately. As pointed out by Eisenberg, "impeding medical research, no less than performing it, has ethical consequences. Not to act is to act."[35] Reversal of the present trend, perhaps through a federally funded insurance program, is necessary for the continued performance of safe controlled-human-exposure studies pertinent to decisions concerning protection of the public against air pollutants.

One limitation of the controlled-human-exposure approach is that it is difficult to study the persons most at risk from air pollutants. There is ample evidence that some groups are most susceptible to the ill effects of air pollution. Excess death reported after the acute air-pollution episodes in London in 1952 occurred predominantly among those with cardiac and respiratory diseases[53,77,109] and mainly in persons 45 yr old and older. Follow-up studies after the acute air-pollution episode in Donora indicated

that those who reported illness during the episode had higher later mortality rates and a higher incidence of disease than those who did not report illness during the episode;[23] this suggests a special effect in the symptomatic group.

Persons with asthma[28] and some persons with other chronic obstructive pulmonary diseases[112] develop greater bronchoconstriction after inhaling dusts, chemicals, and pharmacologic agents than do healthy persons. For this reason, it has been suspected that irritating air pollutants may trigger attacks of asthma. Some epidemiologic studies have suggested this association; others have failed to confirm it.[65] The acute response of asthmatics to air pollutants has been safely studied in controlled-exposure experiments. Further studies are needed to determine the response of this susceptible group to specific inhaled pollutants and pollutant mixtures. A second aspect of asthma that requires special investigation is the hyperactive state itself: How does the varying state of the asthmatic subject alter the response to inhaled pollutants? Nitrogen dioxide has been reported to increase the bronchial responsiveness to carbamylcholine, a bronchoconstricting drug, in some asthmatic subjects.[97] Similarly, ozone has been reported to increase bronchomotor responsiveness in atopic subjects.[56] It is not known whether ambient concentrations of these air pollutants enhance the effect of naturally occurring bronchoconstricting agents.

Air pollutants not only may exacerbate asthma, but may play a causative role. Thus, ozone causes damage to the airway epithelium at concentrations reported in ambient atmosphere[14] and has been shown to cause increased bronchomotor responsiveness in otherwise healthy human subjects[49] and dogs.[75] Influenza virus damages the airway epithelium.[55] Several upper respiratory viral infections seem to trigger asthmatic attacks[70] and increase the bronchomotor responsiveness of otherwise healthy subjects.[37] Possible interactions between respiratory infections and air pollutants require further study.

Children constitute another group of subjects of special interest. Confounding effects of cigarette-smoking are smaller in this group. Furthermore, subtle damage to the lungs and airways during growth may have important delayed effects.

Persons with arteriosclerotic vascular disease are particularly susceptible to the hypoxemic effects of carbon monoxide.

Before controlled-exposure studies are performed on susceptible groups, healthy subjects should usually be studied. The timing of exposure may reveal important information. Thus, subjects can be exposed early or late in the smog season to determine whether adaptatation occurs. Atmospheric temperature appears to play a role in

some effects of air pollution, and this relationship needs to be explored further. Exercise increases the exposure to a given concentration of inhaled pollutant and may alter sites of deposition. The effects of brief exposures to higher concentrations of a pollutant need to be compared with the effects of lower concentrations over longer periods. In addition, the timing of maximal responses to pollutants may vary. For example, the maximal pathologic effect of ozone on lungs occurs 24 h after exposure. Perhaps some physiologic responses are also delayed.

In general, the desirability of experimental exposure of susceptible groups of humans (e.g., children, the elderly, asthmatics) must be balanced against the ethical constraints that should be placed on such experiments on vulnerable populations, even when low-dose exposures are used.

In all studies, detection of adverse effects is limited by the sensitivity of the tests designed to detect responses. Tests of airway narrowing still appear to be the simplest and most useful. However, morbidity and mortality in susceptible persons may be related to susceptibility to infection or related to effects on mucociliary clearance. It is recommended that careful animal experiments be designed to evaluate possible effects on these systems. Specific clues can then be evaluated in humans.

TOXICOLOGIC STUDIES ON EXPERIMENTAL ANIMALS

Studies reporting the effects of chemicals on experimental animals have long been an integral part of the data base assembled to evaluate effects on human health. Responses observed in experimental animals cannot be directly extrapolated to effects on human health, but such studies, if properly designed, do have predictive value and may provide guidelines for the more expensive epidemiologic studies. A bridge between the two may sometimes be built by controlled exposure of human subjects.

Animal toxicology is a particularly suitable, and in some instances the only, method of obtaining information on the effects of pollutants. Studies of long-term effects of pollutants and studies of environmental carcinogenesis require the use of experimental animals. Hypotheses on the mechanisms of action of pollutants are best tested in experimental animals. Effects of nutritional status on responses to pollutants may be examined in experimental animals. An example of the information to be gained this way is the knowledge that vitamin E depletion increases sensitivity to oxidizing pollutants, such as ozone and nitrogen dioxide.

Even peak concentrations of fossil-fuel combustion products in the atmosphere are generally below those for which conventional toxicologic methods are suitable. This has stimulated research over the last two decades on the development of more sensitive toxicologic end points. These include effects on pulmonary function, on lung defense mechanisms, and on clearance of particles from the respiratory tract. Electron microscopy and special staining techniques have increased the sensitivity of pathologic evaluation of pulmonary damage. The application of lung biochemistry to pollution problems is somewhat more recent, but such studies are necessary to yield an understanding of the mechanisms of damage at the cellular level. The full potential of these newer toxicologic techniques will best be realized when they are combined to elucidate the toxic actions of specific compounds or combinations of compounds resulting from fossil-fuel combustion.

The main exposures to fossil-fuel combustion products occur by inhalation when these materials are emitted into the atmosphere. Thus, inhalation is the most appropriate route for exposure of experimental animals. In the case of such materials as fluoride or metallic elements, which accumulate in soil and on vegetation eaten by domestic animals, feeding studies are also warranted. Such materials may cause toxic symptoms in domestic animals and may also enter the food chain and be consumed by man.

Both short-term and long-term inhalation exposure schedules provide useful information. Exposures of 1-4 h are relevant to short-term peaks of pollution. Effects observed after short exposures are not necessarily the same as those evident after long-term repeated or continuous exposures. That is not surprising, inasmuch as effects may arise in the two cases from quite different mechanisms, or biologic adaptation may occur and counteract the acute effects. For example, short-term exposures of an hour or less to sulfur dioxide produce a transient increase in pulmonary flow resistance in some species that is rapidly reversed on termination of exposure. Guinea pigs showed such a response at concentrations well below 5 ppm.[2] In contrast, continuous exposure of guinea pigs to sulfur dioxide at 5 ppm for a year produced no increase in pulmonary flow resistance.[1] The short-term resistance increase results from constriction of bronchial smooth muscle and is blocked by isoproterenol or cooling of the vagus nerve.[83] This would be an acute, not a chronic, effect; chronic increases in flow resistance would result from quite other mechanisms. Even when criteria based on noninvasive techniques are used, long-term chronic studies seldom if ever include measurement of response in the early hours or days of exposure. Such data would provide interesting and useful information on the comparison of acute and chronic responses and on adaptation. In some instances, adaptation is of biologic benefit to an organism; in other instances, it may constitute the loss of an initial protective reflex and be the basis of chronic disease.

Well-designed long-term inhalation studies should have a high priority, especially because it is impossible to use human subjects for such studies. Exposure facilities for continuous long-term exposure, especially those large enough to accommodate primates, require a major capital investment and are expensive to operate. It would appear only proper to locate such facilities in research centers that have expertise in applying and interpreting the sophisticated and sensitive criteria of toxic response, including physiologic, biochemical, and pathologic criteria. This statement does not imply that the investigators should automatically apply every test they can think of on the assumption that something of value must surely result. The end result of such studies is usually a vast array of data that defies rational interpretation.

Respiratory physiologists are currently giving thought to how alterations in pulmonary-function tests may be related to changes in the lung. Such fundamental research deserves high priority. One example of this is the work of Kessler et al.[68] in which alterations in flow resistance and compliance in dogs were correlated with observed changes in airway diameter as observed by tantalum bronchograms. Another example is the correlation of pulmonary function and pulmonary pathology in beagles studied at the University of California at Davis after long-term exposure to automobile exhaust and other pollutants at the EPA laboratories in Cincinnati.[46,60] An important finding by the Davis investigators was that a progressive decrement in pulmonary function occurred over a 2-yr period after cessation of exposure. That suggests that information of value could be obtained by a protocol of more limited initial exposure and study of the animals after exposure. The aim would be to delineate the time and concentration pattern of exposure that leads to progressive functional decrement after exposure. Such experiments would constitute an economical use of existing chamber facilities and of funds.

In vitro studies of pollutants are almost totally concerned with understanding the basic mechanisms of toxic effects. Such information is a necessary precursor for the development of appropriate studies of the toxicity of pollutants in animals and man. The test-tube approach allows careful control of confounding variables in a relatively simple, rapid, and inexpensive manner. Questions can be asked with models of varied complexity, beginning with defined biochemicals and proceeding up to intact organs and tissue-culture systems. Information obtained in such models cannot, of course, stand by itself; further testing in animals or humans is necessary. However, in vitro studies can provide the basis for the appropriate focus of studies in animals and man, particularly with respect to biomolecular effects.

Study and interpretation of pollutant inhalation effects in animals are greatly hampered by the difficulty of evaluating the lung, mainly because of its great structural complexity. Deposition of pollutants in the lung depends on mode of entry, airway diameter and

branching, and anatomic position. These vary greatly among different species. In particular, man generally breathes in an upright vertical position, very different from the horizontal axis of usual laboratory animals. In addition to anatomic factors, the physiologic response of the lung depends on various autonomic and humoral mediators that appear to differ somewhat among species. For instance, there is a wide divergence in the number of histamine-containing lung mast cells.

The biochemical and molecular basis of normal lung function has only recently begun to be studied in depth. This is due in part to technical problems related to the difficulty of preparing and fractionating lung tissue, which tends to be highly collagenous. More importantly, the lung is less homogeneous in its constituents than are many other organs. The multiplicity of lung cell types makes it difficult to interpret changes observed in whole-lung homogenates after pollutant inhalation. For instance, a pollutant effect causing a crucial decrease in a given biochemical intermediate in one target cell may be obscured by the absence of change or even a reciprocal increase in the same compound in other cell types. To understand fully the adverse effects of air pollutants, it will be necessary to improve our knowledge of normal lung cytology, physiology, and biochemistry in animals and man. This requires firm support for basic research in these subjects.

Information is slowly developing along a number of lines. These include the alteration of size and chemistry of pollutants in the airway before they impinge on lung surfaces, the physiology and chemistry of mucus and connective tissue, the biochemical mechanisms involved in normal lung bactericidal activity (which may be subject to alteration by pollutants), and the roles of bronchoactive compounds and the complement system in asthmatic attacks. Some beginnings have been made in providing better means of separating individual lung cell types and subcellular fractions, which should eventually remove many of the difficulties in studying whole-lung homogenates and allow more accurate evaluation of the cellular and subcellular targets of pollutants. All these subjects represent research priorities.

Toxicologic information must be obtained for combinations of pollutants. Combined toxicity that is more than additive (i.e., that constitutes synergism or potentiation) may result from actions in the organism or from chemical or physical interaction of the pollutants themselves in the atmosphere. Similar factors could underlie joint toxic action that may be less than additive (i.e., that constitutes attenuation). An example of biologic interaction is the alteration of the site of deposition or rate of clearance of one material by inhalation of another material, leading to increased or decreased uptake. The effect of inert aerosols on irritant gases is an example of chemical or physical interaction. The response to sulfur dioxide is potentiated by aerosols of trace metals, which promote its oxidation to sulfuric acid, and attenuated

by aerosols of motor oil, which apparently scavenge it to form non-irritating reaction products.

Careful control of the experimental atmosphere is a proper part of any inhalation-toxicology experiment, but it is critical in exposures to combinations of materials. It is not sufficient to introduce substance A into a chamber to produce a defined concentration, do the same for substance B, and then introduce both A and B and assume that the desired concentrations are present. The concentrations of A and B in the mixed atmosphere must be determined by methods shown to be free of mutual interference. Feed systems should be designed so that A and B do not come together in high concentrations before dilution in the exposure chamber. The confusion related to combined exposure to ozone and sulfur dioxide was resolved only when it was found that mixing of the two gases at high concentrations in the feed system had led to the formation of sulfate, which had gone undetected.[7] Relative humidity and residence time in the exposure chamber can also affect the potential for chemical interaction of pollutants, so they must be taken into consideration in combined exposures.

Toxicologists who study combinations of fossil-fuel combustion products must not think and work solely within the confines of their own discipline. They must develop a mutual understanding and cooperation with combustion engineers and atmospheric chemists. It might be added that some feel strongly that the problems of health effects of fossil fuels will ultimately be understood only when epidemioloists are in a position to understand and use the joint findings of these other disciplines.[3] For example, the nature of metallic particles that coexist with sulfur dioxide appears to govern the chemical nature of the resulting sulfur-containing aerosols, and this in turn governs the biologic response. Atmospheric chemists have shown that some trace metals tend to concentrate in smaller size fractions of urban aerosols and that some tend to accumulate at surface layers of particles. In both cases, the large surface areas would have a potential for interaction with gaseous pollutants. In the latter case, the biologic activity of the particles could well be greater than would be suggested by the total mass loading of a specific trace metal. Investigations of combustion conditions leading to formation of such particles should proceed with assessment of their toxic potential alone and in combination with gases, such as sulfur dioxide.

Two approaches have been used in the study of mixtures of pollutants. In one, the effects of individual pollutants are assessed by the chosen criteria and then by consideration of the effects of two or more specific pollutants given together. In the other, a mixture of pollutants occurring in urban atmosphere is used.

The first has the potential to define specific interactions and relate them to toxic response. It is thus usually possible to interpret results in a useful manner. However, it remains questionable whether other pollutants present in the urban atmosphere but not in the experimental atmosphere would have influenced the observed course of events, and, if so, how.

The second approach has the advantage of presumably examining the situation as it actually is for populations exposed to urban pollution. Unfortunately, however, the only conclusion that one can draw from any of these studies is that air pollution is harmful to animals; and we already know that it can be harmful to people. It is often impossible to determine which pollutant or combination of pollutants was most critical in producing whatever detrimental effects were observed. As long as criteria documents and air-quality standards and control measures deal with single pollutants, results of the experiments on simulated mixtures will prove difficult to interpret in that context. To the Committee's knowledge, none of the experiments to date that have used complex simulated atmospheres has revealed any particular toxic effect that had not been observed as a response to one or another of the components. It has been suggested[90] that the observed toxic response to ozone appears to account for the observed effects of complex experimental mixtures of photochemical oxidants. Appropriate experimental design can aid in determining the effects of specific components of complex mixtures. For example, the design of the EPA studies in Cincinnati attempted comparisons between such factors as irradiated and nonirradiated automobile exhaust with and without added sulfuric acid, etc.; although mixtures were used, the effects of individual components could be examined. Careful thought should be given to protocol and to eventual interpretation of results before major funding is committed to long-term chronic studies that will use "simulated urban atmospheres."

Another aspect of combined toxic action in need of investigation is the effect of sequential, as opposed to simultaneous, exposure to pollutants. One compound particularly worthy of attention in this regard is ozone. Exposure to ozone, even in concentrations that may occur in the ambient atmosephere, can render the lung more sensitive to bronchoconstricting agents.[56,97] Whether such exposure also increases sensitivity to other irritant pollutants is not known.

The development of models of disease in experimental animals is another type of fundamental research that should have the potential to provide useful information when combined with inhalation toxicology. Similarly, any information on why a given animal or a given species is particularly sensitive to a given pollutant would be valuable.

RECOMMENDED RESEARCH

Well-designed long-term inhalation studies are a high-priority need. They would be best located in research centers that have expertise in applying and interpreting physiologic, biochemical, and pathologic criteria of response.

High priority should be given to basic research on the lung, including relationships between alterations in pulmonary fuction and pathologic changes in the lung, as well as basic studies of lung biochemistry and cell biology.

Toxicologic information on combinations of pollutants is vitally needed; knowledge in this field is sparse. Control of exposure-chamber atmospheres is critical. Failure to observe this deepens, instead of lessening, confusion about joint toxic action. Interdisciplinary research--with toxicologists, combustion engineers, and atmospheric chemists working together--appears to be the most appropriate way to approach this overall problem.

In designing studies of mixtures that "simulate urban atmospheres," careful thought should be given to how the results will be interpreted and used in standard-setting.

Other approaches with the potential for yielding useful and needed data are related to the effect of sequential exposure to pollutants, the development of models of disease in experimental animals, and the question of why a given animal or species is especially sensitive to a given pollutant.

IV

SPECIAL POLLUTANT ISSUES

TRACE ELEMENTS

The 1975 Indian Wells report[26] indicated that there were insufficient data to evaluate the potential health effects of the trace elements associated with fossil-fuel combustion. It set research priorities that included characterization of the trace elements in emissions, determination of their environmental concentrations and chemical states, and acquisition of data on some elements with respect to effects on humans.

This assessment remains valid, despite the many cogent studies and reports that have since been issued. A host of government documents clearly support--indeed, mandate--trace-element studies.[27,61,119,121,124] Several valuable workshops and treatises[6,11,19,30,57,126,128] and many research reports are relevant especially for trace-element characterization. Collectively, these documents broaden the information base for trace elements and foretell important data. Nevertheless, the current data base, however it will be augmented soon, is inadequate.

Our assessment of occupational- and public-health risks associated with trace-element release and fossil-fuel combustion included the composition of fossil fuels and their combustion products, environmental sampling and monitoring, data on humans, and experimental toxicologic studies.

TRACE ELEMENTS IN COAL AND COAL COMBUSTION PRODUCTS

In 1974, van Lehmden *et al.*[130] reported that interlaboratory analyses of fossil fuels, mainly coal, revealed large variations in trace-element composition that proved to be methodologic. Later, in another large interlaboratory effort sponsored by the EPA in cooperation with the National Bureau of Standards (NBS), analytic methods were reevaluated; reference materials on standardized coal (SRM 1632) and fly ash (SRM 1633) were established. These well-analyzed materials can serve as an analytic "norm" and as a prototypic coal for use in models. The average concentrations of 37 elements in the coal and 41 in the fly ash were determined; roughly seven-eighths qualify as trace elements.[96]

Compositional Data

The trace elements in SRM 1632 coal at 1-10 μg/g are scandium, cobalt, arsenic, selenium, antimony, cesium, samarium, thorium, and uranium; those at over 10 μg/g are chromium, manganese, nickel, zinc, bromine, lead, strontium, barium, lanthanum, and cerium. Those occurring in fly ash at 1-10 μg/g are antimony, iodine, cesium, europium, terbium, ytterbium, hafnium, tantalum, and tungsten; those at over 10 μg/g are scandium, vanadium, chromium, manganese, cobalt, nickel, zinc, arsenic, selenium, bromine, rubidium, strontium, yttrium, zirconium, barium, lanthanum, cerium, samarium, lead, thorium, and uranium.[96]

The foregoing data reveal fly-ash-to-coal enrichment factors of between 8:1 and 9:1 for nonvolatile elements; they do not take into account the portions of the volatile elements--e.g., zinc, arsenic, and selenium--that do not completely condense on fly ash. The interlaboratory results, all reflecting state-of-the-art methods, often had relative standard deviations (normalized data) greater than 25%. Data on some elements--such as mercury, fluorine, molybdenum, and beryllium--that are ecologically and toxicologically important are missing. Moreover, these valuable compositional data omit information on the chemical forms and oxidation states of the trace elements--highly important toxicologic determinants.

There are coal and fly ash compositional data from other laboratories pertaining to volatile-element emission and to some of the elements unmeasured in the EPA and NBS standards. In any case, measurements of both types of trace elements contain major analytic uncertainties and deficiencies.

Output Estimates

Mass-balance studies of some trace elements have been achieved: mercury balances[10,67] and balances on 15-41 trace elements in a coal-fired power plant.[15,16,66,69] These mass-balance studies are important in determining the composition of slag, inlet and outlet fly ash (before and after emission control), and fuel-gas components of burned coal in modern plants.

If 10^9 tons of NBS standard coal were burned annually (a rate close to current U.S. consumption), the estimated trace-element release to the environment, on the basis of the analysis of Bolton *et al.*,[15,16] would be around 10^3-10^4 tons/yr for most of the important trace elements. According to the discharge data from modern coal-fired power plants with new electrostatic air cleaners, 90-99% reductions in trace-element emission can be contemplated. Reductions in emission of the more volatile elements--such as arsenic, lead, and selenium--are the least effective.

Radionuclides

Several naturally occurring radionuclides are found in coal: potassium-40; thorium-228 and -232; lead-210 and -212; radium-224, -226, and -228; polonium-210; radon-220 and -222; and uranium-234, -235, and -238. McBride *et al.*[78] estimated the curies per year released from a 1,000-MW(e) coal-fired power plant having 99% emission control. With respect to a hypothetical population residing within 90 km of the plant, they indicated that the major population dose would result from radium-226. Coles *et al.*[25] traced the fate of many of these radionuclides in the slag and fly ash of two comparably controlled plants--one burning low-ash coal, the other burning high-ash coal containing these elements at concentrations about 3.3 times higher. The radionuclide abundance in both coals was consistent with secular equilibrium. After combustion, postprecipitator fly ash from the high-rank coal showed a 5-fold enrichment factor for uranium, thorium, and radium, whereas bottom ash was enriched about 3.5-fold. This increased enrichment in emitted fly ash suggested some volatility --a view supported by particle-size fractionation of the fly ash that revealed high enrichment factors (7:1-9:1) in the smaller fractions, especially for uranium, lead, and radium. These volatile elements are ascribed to the uranite content of coal, with uranium trioxide being the volatile form of uranium. Uranium originally associated with silicate (coffinite) appears to be nonvolatile; therefore, the fly ash enrichment factor for uranium is higher for low-ash than for high-ash coals. If there is a potential health problem from these radionuclides, it will undoubtedly be associated with coal high in uranium and thorium, e.g., over 5 ppm. The coal rank will further modify the emission:slag ratios of these elements, so resolution of the radionuclide problem may depend on the comparative technologies of slag-fly ash disposal and emission control.[25]

Other studies have extended the association of some trace elements with organic and mineral fractions of coal, fly ash emission according to particle size (i.e., as a function of particulate surface area), and enrichment factors in different combustion products.

Leaching Behavior of Combustion Wastes

Investigations into the leaching behavior of trace elements from coal slag and fly ash have given new insight into the potential environmental problems arising from soil and water contamination.[58,126] For a perspective of the risks, the extant geochemical environment and its known health consequences must be appreciated.[11,57] Pertinent studies have been reported on urban air, soil, and water and on the origins, accumulation, and environmental persistence of trace elements.[33,48,51,64,80,125,135]

With these background data, the impact of leachates and process waters on the local environment, including biota and aquifers, can be studied. Many solid-waste disposal processes are being evaluated (for example, see Vol. 1, Sec. 4 of Brainstein *et al.*[19] The transport and transformation pathways of hazardous chemicals from solid wastes were subjects of the 5th Annual LASL Life Science Symposium held in Los Alamos in October 1977[127] and were stressed in the 1978 Workshop on Health and Environmental Effects of Coal Gasification and Liquefaction Technologies (Federal Interagency Committee on Energy Technologies).[5] From such sources, it is evident that all coal-combustion and coal-conversion processes give rise to effluent liquid and solid wastes that entrain and concentrate most of the trace elements, particularly those which are not highly volatile. Some of the effluents, such as wastewater, may require disposal in ash basins and landfills, and environmental control may be based primarily on site location. The latter probability indicates the need for extensive investigations into the behavior of soil toward leachates, the leaching behavior of wastes, the action of acid rains on heavy metals in soils and solid wastes, the effects of metal interactions on biotic uptake, and many aspects of hydrologic science.

TRACE ELEMENTS ASSOCIATED WITH OTHER FOSSIL FUELS

An EPA report on public-health implications of using coal as an alternative to gas and oil[41] indicated that the use of coal increases the emission of many trace elements, on the basis of comparable BTU output, 10- to 100-fold. For boron, cadmium, chlorine, fluorine, lead, chromium, cobalt, copper, and zinc, the factors are larger, because oil appears to have negligible intrinsic concentrations of these. The vanadium and possibly nickel concentrations are frequently much greater in oil; therefore, conversion to coal may decrease their output.

When shale oil is separated from raw shale by retorting, most trace elements are retained in the spent shale.[111] Arsenic, nickel, cobalt, molybdenum, and chromium partly transfer to the shale oil--arsenic at about 5%, the remainder at 0.1-1%. Evidence of slight contamination of retort water with boron, copper, fluorine, and selenium (0.1-3 ppm) was found. Data on mercury were not reported, because the attempted mass balance was unsatisfactory. Gas-phase effluents--largely, arsenic and mercury--were not detailed, but were stated to account for 3% by weight of the totals, compared with 1.2% for retort water. Thus, except for the more volatile elements, controlled shale-oil combustion will likely discharge trace elements at much lower concentrations than controlled coal combustion. The spent shale, however, may pose a serious disposal problem, owing to the substantial enrichment in most trace elements and its extraordinary porosity (surface-area) factors, which portend soil and water contamination.

Coal-gasification research at carbon dioxide-acceptor pilot plants have included mass-balance studies.[105] Direct analysis of the quenched product and regeneration gases indicated that the following approximate percentages of the intake concentrations of trace elements were present: boron, 0.6; cadmium, 3.2; mercury, 21; chromium, 6; arsenic, 2; selenium, 1; vanadium, 2; antimony, 2; chlorine, 15; and lead, 2. However, major mass-balance deficits were again noted for the highly volatile elements, specifically, mercury, lead, selenium, and boron. The intake concentrations of the trace elements were determined largely by the fossil fuel (coal or lignite) used, but the carbon dioxide-acceptor material (calcium oxide) did contribute significantly to the concentrations of cadmium, halogens, selenium, and uranium. The quench waters used in purification of product and regeneration gases appeared to recover substantial amounts of volatile elements--e.g., mercury, 78%; cadmium, 45%; selenium, 30%; arsenic, 24%; and fluorine, 30%. This suggests that the unquenched gases initially contained most of the volatile components from the fossil fuel. These recoveries are probably overestimated, however, owing to the mass-balance problem cited.

Emission analyses from coal-gasification processes have revealed that trace-element concentrations in regenerator flue gas are about the same as those in the flue gas from coal-fired power plants.

The process quench and scrubber waters and the process solid wastes, both containing large quantities of trace elements, are destined for evaporation ponds and landfills. Laboratory studies of the permeation and leaching characteristics of these wastes have indicated a potential groundwater contamination problem.[105]

TRACE ELEMENTS IN THE ENVIRONMENT

Needed information on the environmental concentrations of trace elements in regions around coal-fired power plants has been reported by Horton et al.[58,59] Of 29 trace elements measured in fly ash (1.5-28 km from the emission sources), barium, beryllium, copper, mercury, selenium, and strontium were found to concentrate in soil; beryllium, cobalt, molybdenum, strontium, and vanadium concentrated in vegetation; and cobalt and manganese concentrated in groundwater.

The Oak Ridge National Laboratory overviews of coal-conversion technology[19] devoted much attention to trace elements in the environment. Information on their physicochemical states is usually lacking, and the seriousness of this deficiency is underscored by Table 6.45 of the report, in which 13 chemical forms of arsenic, 14 forms of sulfur, and five forms of mercury were identified as freshwater pollutants.

These collective efforts, although important, are only the beginning of an attack on an immense problem; they indicate that environmental monitoring is far from satisfactory. A valuable data base on trace-element concentrations and speciation around fixed sites is accumulating; these data, with background information on atmospheric, soil, and water concentrations and on natural enrichment factors,[13,29,33,45,64,80] should provide much of the rationale for environmental surveillance.

ASSESSMENT OF TRACE-ELEMENT EXPOSURES OF MAN

Present capacity to identify and assess exposed populations around fixed sites of fossil-fuel use is difficult to gauge, because there seems to have been little or no demonstrable effort to do so. Obviously, this problem is very broad and is not limited to trace elements. The best estimates for use in determining occupational and public-health effects of fossil-fuel combustion products continue to be derived from prospective theoretical models that are largely untested and that harbor inconsistent viewpoints. The result is order-of-magnitude differences in estimates.[34,133]

Probably the best of these models is that of Vaughn et al.,[129] which deals with emission, transport, and deposition of trace metals from a coal-fired power plant. This model was central to the decisions and recommendations made by a recent workshop on health effects of coal combustion.[128] On the basis of estimated outputs, "market-basket" analyses, water and occupational standards, current ambient concentrations, and the intrinsic toxicity of some trace elements, the workshop cited nickel, cadmium, chromium(IV), arsenic(III), and fluoride as having potential health effects. Another model of special relevance to trace-element assessment is that of Booth and Kaye,[17] used by McBride et al.[78] to estimate the radiologic impact of coal-fired power-plant effluents.

The devastating human experience with alkyl mercury poisoning may be of value in planning trace-element research. Several mercury compounds, inorganic and organic, are discharged into air, soil, and water from diverse industrial, agricultural, and mining activities. These forms of mercury also occur naturally. Their toxicology indicates risks from direct exposures and through accumulation in the food chain.[92] A bioassay for human exposure has been developed that depends, inter alia, on hair analyses. The environmental fluxes and conversions of mercury have required special study and development of new analytic methods. The interplay of mercury with other trace elements, such as selenium, has also necessitated new evaluation methods.

Epidemiologic studies of trace-element exposures have been reported,[24,43,44,47,84,87] but few pertain to fossil-fuel use.

However, the report of Bencko, Symon, and co-workers[8,9] on the health problems associated with a coal-fired power plant using high-arsenic coal (about 220 ppm) is of special interest because of its direct relevance. In this study, the best indicator of exposure was human hair. Urinary concentration was useful for assessing daily intake. The epidemiologic findings and allied environmental data indicated an underlying problem of high indigenous arsenic concentrations and unique topographic and meteorologic relationships to the exposed population. Although the value of these data for modeling human exposure from U.S. power plants is problematic, these kinds of special factors can be expected to complicate most fixed-site assessments and limit modeling efforts.

Most epidemiologic research pertains to mercury, lead, and cadmium, probably because of historical interest in these metals and because their adverse health effects continue to be widespread among workers and the public. A recent NRC panel on mercury nevertheless concluded that "data are still incomplete and the technical and medical proficiency too limited to assess conclusively the effect of chronic low exposure to low levels of mercury pollution on human beings, as well as lower orders of the food chain and the environments."[92] A similar evaluation applies to cadmium and lead.

The International Commission on Radiological Protection Reference Man[62] is the most extensive source of dietary-intake and tissue-content values for the trace elements. This compendium and others (such as that by Iyengar et al.[63]) are important resources for assessing exposed populations.

TOXICOLOGIC STUDIES OF TRACE ELEMENTS IN MAN AND LABORATORY ANIMALS

Several agencies are supporting research on trace elements as factors in human disease. The emphasis appears to be on animal studies of lead, mercury, cadmium, nickel, chromium, arsenic, selenium, vanadium, fluorine, and beryllium. These choices cannot be criticized, but the emphases may unbalance the data. Human and laboratory-animal studies on a number of trace elements have been recently reported.[12,21,22,79,101-104,115] It is not surprising that most of the new experimental studies are related to cadmium, lead, and mercury.

The number of human studies reported is substantial; this probably reflects the development of highly sensitive analytic methods. Long-term feeding studies and metabolic studies on prenatal, neonatal, and adult animals seeking developmental, reproductive, and genetic effects are both reassuring and indicative that trace-element toxicology is being widely appreciated as a high-priority

research subject. Complementing this surge in trace-element research has been the emergence of a number of books on trace-element toxicology.[42,44,52,76,93-95,118,120]

Despite the encouraging developments, there is clearly a deficiency in low-concentration chronic-exposure studies. Because identification of elemental species in emission and leachates is inadequate, ingestion and inhalation studies on these specific physicochemical forms are severely constrained. Elements--such as cadmium and arsenic--with suspected carcinogenic, embryotoxic, and teratogenic effects require special long-term investigation in several animal species (see Chapter V).

RECOMMENDATIONS FOR RESEARCH

- Measurement and characterization of trace-element emission should be intensified, emphasizing secondary pollutant formation, speciation, and vapor- and particulate-phase relationships within 0.01-100 km of stacks or other fixed sources.

- Solid and liquid residues--e.g., precipitated fly ash, slag, and retort, quench, and scrubber waters--should be studied to determine the nature and leachability of trace elements and metallo-organic substances, such as alkyls of arsenic, mercury, selenium, and lead.

- Studies of environmental concentrations and forms of the trace elements should continue, to afford insight into bioconversions, bioaccumulation, and food-chain incorporation in particular. In the context of these recommendations, the physicochemical states and abundance of arsenic, chromium, nickel, cadmium, and beryllium are especially important, because these metals probably contribute to carcinogenesis. The oxidation states of arsenic and chromium need special attention, because arsenic(III) and chromium(VI) differ markedly in their carcinogenic potential from arsenic(V) and chromium(III).

- Transport and distribution models are required for estimation of trace-metal concentrations in the biosphere and of effective human-exposure concentrations with respect to fixed emission sources. Because order-of-magnitude variations are currently implicit in basic model components--e.g., atmospheric dispersion--their validity and appropriateness are crucial. Evaluation of these transport models should be undertaken, and comparisons made with fixed-site sampling and personal monitoring.

- Toxicologic studies should be undertaken in laboratory animals and should emphasize long-term low-concentration exposures

to specific physicochemical forms of the trace elements. These forms should be prototypic--i.e., represent highly retained and highly labile forms in vivo and thereby, it is hoped, set boundary conditions--or be based on identified species in emission wastes before and after biospheric conversion. Animal research should be directed to important gaps in information on pulmonary and gastrointestinal absorption, distribution and metabolism, biotransformation, and elimination and should be supported wherever possible by histologic and biochemical assessments.

- Animal studies directed at synergistic actions among trace elements, between trace elements and other pollutants, and between trace elements and ionizing radiation deserve high priority. Cell proliferation, metaplasia, tumor induction, immunologic response, tissue repair, and carcinogenesis are of special importance, particularly with respect to the respiratory system and other target organs, depending on the elements.

- Human investigations should be given the highest priority. Short-term pharmacokinetic studies of trace elements for which there are sensitive detection methods should be considered. For example, there are suitable radioisotopes of cadmium, mercury, lead, and selenium, which should permit studies at less than nanogram concentrations.

- Epidemiologic studies of populations around operating and projected power plants and fuel-processing sites are needed. Indicators for human-exposure assessments should be developed from the epidemiologic data and experimental studies. Identification of the so-called "critical group" is important, because control of this group may lead to control of the areal population.

ATMOSPHERIC TRANSFORMATION AND TRANSPORT OF EMITTED POLLUTANTS

To describe the damage to human health and the environment from fossil-fuel combustion products, one needs to know the concentrations of air pollutants to which the population at risk is exposed. This requires a quantitative understanding of the atmospheric processes that act on emitted pollutants. These processes are emission of other materials, transport and dispersion, chemical and physical transformation, and removal by dry and wet deposition.

Only if these processes are understood can population exposure to atmospheric energy-related (AER) pollutants be accurately predicted and the effects of alternative energy strategies be assessed. Such predictions are achieved through computer modeling that encompasses all the above processes and that rests on laboratory experiments and field studies. This section outlines the subjects in which research is most required to advance understanding of what governs population exposure to AER pollutants.

EMISSION

The principal health-related pollutants resulting from fossil-fuel combustion are nitrogen oxides, sulfur dioxide and sulfates, hydrocarbons (including polyaromatic hydrocarbons) and other organic compounds, and particles (aerosols) consisting of matrix, trace elements, and high-molecular-weight hydrocarbons. The specification of the source strength and physical and chemical states of these emitted materials is a key to an understanding of their fate and of human exposure to them. Emission of sulfur dioxide is now well understood, it being the fate of most (about 95%) of the sulfur in fuel in the absence of treatment. A small fraction of fuel sulfur is directly oxidized to sulfuric acid vapor and to metal sulfate aerosols. Instrumentation has recently been developed that measures source strengths of these components;[31,32] however, the combustion processes affecting such emission are not yet understood, so more extensive field measurements are required. Sulfur dioxide emission is greatly diminished by scrubbing or removal of sulfur dioxide from postcombustion gases; development of inexpensive reliable monitors of scrubbing efficiency is needed. Scrubbing may also be expected to decrease greatly the sulfate and nonsulfate aerosol component of emission. Research is required to learn how these processes work and to predict changes in aerosol emission that result from the widespread practice of scrubbing.

Nitrogen oxide emission results from oxidation of fuel nitrogen and from high-temperature fixation of atmospheric nitrogen. Almost all fuel nitrogen is released as oxides of nitrogen (NO_x); the amount of atmospheric nitrogen that is fixed depends heavily on combustion conditions, including excess air at the combustor, local temperature, concentration and temperature fluctuations, and rate of cooling of the hot combustion gases. Better understanding of these processes should lead to improved combustor practice. In the meantime, a much more extensive network of NO_x emission monitors is required to provide data for model calculations.

Emission of organic compounds results from incomplete (hence, inefficient) combustion, and such emission from modern, highly efficient facilities is relatively minor. Major concerns are polyaromatic hydrocarbons (PAHs) that are relatively stable thermally (structurally similar to graphite). These compounds differ significantly among themselves in reactivity and bioactivity. Emission of PAHs may be expected to increase with insufficient air, which may be used to control NO_x and sulfuric acid emission. Research is required to specify source strengths of these compounds by combustor type and operating condition. Fugitive hydrocarbon emission from coal conversion (gasification and liquefaction) may be significant; research is needed for qualitative and quantitative specification of this emission. Occupational exposure may be significant.

Emission of aerosols (particles) from combustion activity has long been worrisome. Today, such emission is largely controlled by means of mechanical devices, e.g., cyclones, electrostatic precipitators, and, occasionally, fabric filters. Control efficiency is specified by mass. But such specification is inadequate, because the readily controlled large particles (over 5 μm) contribute the overwhelming proportion of the uncontrolled mass emission, whereas the smaller particles (less than 2 μm, down to submicrometer range) persist longest in the atmosphere and have the greatest ability to penetrate into human airways. The chemical composition of emitted aerosols, particularly the surface composition, depends on their chemical history and is not well understood. The smaller aerosols present disproportionately more surface and thus serve as a condensation or adsorption site for effluent species initially present in postcombustion gases. D. Natusch (Colorado State University) has shown that PAHs adsorb onto aerosols in the rapid cooling at the stack mouth. Similarly, R. Smith (Battelle, Pacific Northwest Laboratory) has shown layering of materials on aerosols with concentration of relatively volatile materials (e.g., arsenic trioxide, As_2O_3) at the surface. Research is required to understand what governs the amount and chemical composition of emitted aerosol as a function of particle size.

TRANSPORT AND DISPERSION

Transport and dispersion determine the concentration of material at a given point that results from a given distribution of emission, in the absence of transformation and removal.

There is need for research on transport and diffusion processes to understand and characterize better their effects on air quality. Formulation and verification of improved air-quality and associated meteorologic models that more realistically represent the interactions of transport and diffusion, especially on the regional scale, should be a research goal. Improvements in and verification of the accuracy of these types of models in turn require improvements in numerical methods; better characterization of turbulence, including chemical reactions in turbulence; development of remote satellite sensing of atmospheric pollutants; computer advances; better characterization of cloud processes; better characterization of atmospheric thermodynamic and dynamic variables; development of discrete small-scale constituents for models; better characterization of population exposure in polluted areas; and better discrimination between man-made and atmosphere-generated pollutants.

Initially, the heat content of emitted pollutants is responsible for buoyant plume rise. However, transport and dispersion can be considered as largely uncoupled from the trace-chemical composition of the atmosphere (an exception can be an optically dense pollutant that affects heat balance).

The atmosphere undergoes turbulence, a complicated process. The characterization of turbulence is essential for understanding the transport, mixing, and spreading properties of AER effluents emitted into the atmosphere. The usefulness of current theories of pollutant transport, mixing, and spreading (diffusion) is restricted by our limited ability to understand and characterize turbulence. Whereas current semiempirical approaches to the description of turbulence as related to diffusion have been useful, this usefulness has been restricted to the description of the evolution of inert tracers or linearly reacting chemical and radioactive species in homogeneous (simple) situations. Often, the most important circumstances needing characterization are of nonlinearly reacting chemical species in complicated nonhomogeneous situations; research in this subject is clearly needed. Transport and dispersion processes dominate the consideration of population exposure from a given set of emission sources. These processes admix AER pollutants from different sources with trace atmospheric constituents resulting from other activities (e.g., industry) and from natural sources. These turbulent mixing processes determine the later chemical reactions of AER pollutants. A well-known and well-understood example is ozone destruction (by nitric oxide) and formation (by photochemical smog reactions); but this dependence of chemistry on mixing is quite general. Turbulence governs the mixing rate of initially segregated pollutants (e.g., AER plumes injected into background concentrations) and the potential reactions. Furthermore, turbulence tends to be intermittent. The processes need clarification and practical characterization.

Dominant atmospheric processes that determine pollutant concentrations include the rate at which the material from a stack spreads horizontally and vertically and the height of the mixed layer (the atmospheric layer adjacent to the surface, in which turbulence, usually thermally induced, mixes pollutants). Almost all useful theory on vertical spread of pollutants and growth of the mixed layer is for conditions over smooth terrain, which is horizontally homogeneous; research is needed on how to predict the spread of pollutants over the irregular surface in urban and suburban areas.[4,54] The diurnal variation of turbulence in the mixed layer is especially important.

For the transport of pollutants over long distances (more than 100 km), knowledge is poor on how trajectories and stability of air panels are affected by terrain (e.g., over coastal regions and mountain ranges) and by mesoscale and larger meteorologic systems (e.g., sea breezes, frontal systems, and storms). Continued research is required on a regional and continental scale and on chemical and meteorologic modeling. Such work is required at the very least to incorporate research results into transport and transformation modeling. Research is also required on improving

techniques for modeling. There must be continued efforts in model validation by means of field measurements.

Formulation of new air-quality and meteorologic models is needed to measure the emission, transformation, evolution, and fate of AER pollutants under a broader variety of situations. Many existing models are not well formulated and lead to unrealistic results. For example, conventional eddy diffusivity, wherein atmospheric transport due to turbulence is treated as a diffusion process, breaks down in the highly convective atmospheric boundary layer and over complex terrain. Once realistic models are formed, in mathematical terms, a major constraint in their practicality is the ability to solve the resulting complicated mathematical (partial differential) equations efficiently and accurately. Currently, the usefulness of even properly formulated models is limited by the means to solve such equations. Methods of solution, known as numerical methods (e.g., discretization or finite-difference methods), need improvement to minimize errors and to increase computer speed of solution. Although numerical methods research in the past has been directed to solving classical meteorologic problems, air-quality models treating the evolution of many chemical species with high nonlinear and time- and space-varying phenomena pose new problems. Improvements in computer speed, storage capacity, and architecture (e.g., parallel processing and a general ability to cope with large data arrays and flows) would increase the usefulness of computer-oriented models in treating AER problems realistically.

Perhaps the most useful method for characterizing the evolution of AER pollutants and exposures would be formulation of probability density functions for the concentration and evolution of AER species. Enough work has begun in this direction to indicate its promise for future research.

There are poor meteorologic data on many areas of the world. Meteorologic models using available data with terrain data and equations of physical constraint are under development to diagnose the complete three-dimensional space- and time-varying thermodynamic and dynamic fields. This work should be extended to provide for timely synthesis of regional-scale atmospheric processes in a way suitable for use in air-quality models and analyses.

A computer connection between Brookhaven National Laboratory and the National Meteorological Center (of the National Oceanic and Atmospheric Administration) is providing the potential of pollutant forecasts and timely air-quality postanalysis. Real-time trajectory and AER pollutant forecasts are under development at Brookhaven National Laboratory. Such forecasts could aid in air-quality and epidemiologic field studies, as well as provide warning of forthcoming air-quality trends.

Earth-orbiting satellites can monitor the earth's atmosphere. Little of their considerable potential for monitoring evolution of AER gases and particles has been investigated or implemented. With further study, satellite sensing of atmospheric gases, particles, and weather phenomena could lead to important improvements in characterization of regional, national, and international transport over the globe.

CHEMICAL AND PHYSICAL TRANSFORMATION

It has been recognized for some time that primary (i.e., directly emitted) pollutants may react in the atmosphere to form more noxious materials. Major research activities have been directed at the formation of photochemical oxidants (principally ozone) from reactions of NO_x and hydrocarbons and at the formation and chemical and physical evolution of aerosol sulfates from sulfur oxide. The present extent of research in these subjects would appear adequate if it were continued over the next several years, but there remain troublesome uncertainties in rates and mechanisms of these processes. Unless these processes are clarified, it may be impossible to assess the effects of alternative strategies accurately. Research is needed on ozone and other oxidants, including the processes governing the concentrations of free radicals (hydroxy and hydroperoxy), the role of natural versus anthropogenic hydrocarbons, and competitive processes for nitrogen oxide oxidation (i.e., free-radical versus in-cloud, aqueous-phase oxidation of nitrogen dioxide to nitric acid).

Research is needed on sulfur dioxide and sulfates--the role of heterogeneous transformation processes (such as sulfur dioxide oxidation; interactions of sulfur dioxide, ozone, and water; interactions of sulfur dioxide, hydrogen peroxide, and water; and sulfur dioxide oxidation on graphic materials and other aerosols), aerosol transformation (nucleation, growth, and gas-aerosol reactions), and reactions of sulfur dioxide with free radicals (hydroxy and hydroperoxy radicals and organic radicals).

Research is needed to measure concentrations of nitric acid vapor, which is now thought to be a significant, common pollutant.

Aside from sulfur dioxide, NO_x, and oxidants, there are important research needs that should be addressed, such as interactions of nitrogen oxides with organic compounds to form potentially carcinogenic nitro and nitroso compounds, formation and reactions of organic aerosols, and chemical sinks of polyaromatic and other organic compounds. Research in these subjects must integrate laboratory and field studies. In many cases, adequate instrumentation must be developed. The most useful instrumentation for field programs is reliable real-time equipment; significant advances may be expected from the use of modern optical techniques, such as those with lasers.

There is a need for theoretical studies, especially of the interaction forces that govern aerosol growth.

REMOVAL PROCESSES

"Removal processes" means the ultimate sink whereby the materials in question are removed from the atmosphere. These processes are immediately subdivided into wet (i.e., in-cloud or in-rain) and dry deposition. Considerable research is under way in these subjects and must be continued. Laboratory studies on both fundamental properties (e.g., Henry's law coefficients) and more empirical phenomena (e.g., "sticking coefficients") are necessary. Necessary field studies include dry-deposition studies (on eddy correlation, relation to plant stomatal activity, surface moisture, etc.) and wet-deposition studies (on gas-phase and aerosol concentrations vis-a-vis cloud and rain processes). It should be stressed that deposition rates depend not only on the rates of atmospheric dispersion that brings materials to the surface, but also on specific chemical interactions that vary from compound to compound and that must therefore be determined for all compounds of concern and for aerosols as a function of size.

ANALYSIS AND MONITORING

To determine the effect of fossil-fuel combustion on the quality of air, it is necessary to be able to analyze air samples for gases, chiefly sulfur dioxide and nitrogen oxides, and aerosols, chiefly sulfuric acid and sulfates in various chemical forms having particle sizes less than 2 μm and other particles greater than 2 μm.

By far the most attention has been paid to the various chemical species of sulfur. Until the early 1950s, the chemical species considered to be of primary importance was sulfur dioxide. Many methods were developed for analysis of sulfur dioxide in ambient air. It is the only sulfur compound for which federal and other standards have been promulgated. A standard method for analysis has been adopted, and analyses are made at many stations across the United States. The primary purpose of the analyses is to determine whether the federal standards for sulfur dioxide in ambient air are being exceeded.

The available methods of analysis for sulfur dioxide in ambient air are entirely adequate when they are applied with due consideration of possible interferences. Many substances that may be present with sulfur dioxide can perturb an analytic method, and variations in air quality for which corrections are not made may cause serious errors. Any attempt to measure sulfur dioxide in air must use a method suitable for the air quality of the area in question. Sulfur dioxide analyses may be virtually meaningless if other pertinent components of the air are not identified within specified limits. Therefore, routine sulfur dioxide analyses may have little validity in the absence of frequent checks on the presence of interfering substances and adjustments in the analysis to accommodate such variations. Frequent calibrations of apparatus and procedure with standards are important, but they do not deal with fluctuations in interfering substances. High temperature has also been found to interfere with the West-Gaeke procedure for the analysis of sulfur dioxide.

Since the early days of concern with air pollution, when the main indexes of pollution were the concentrations of sulfur dioxide and visible particles, awareness has heightened that these substances may very well not be the ones with a major impact on human health. More attention is now being given to transformation products of sulfur dioxide, mainly sulfuric acid and sulfate salts, and to fine particles that are present in air as stable aerosols. As the emphasis has shifted, it has become necessary to find methods to identify and measure these forms of sulfur and to assess the particle size distributions and chemical speciation of particles in these aerosols.

Analysis of total sulfate in particles is relatively simple and has been done routinely for many years. Because sulfur dioxide may be converted into sulfate on the surface of the collector, a total-sulfate analysis may not be representative of the actual sulfate content of the air. Assay of ambient air for total sulfur (that present as sulfur dioxide and that present as sulfuric acid and

sulfates) is direct and insensitive to interferences from other materials; the commonest problem in the analysis of sulfur dioxide is the conversion of some of it to sulfate.

However, total-sulfate or total-sulfur analysis is of little value in assessing health effects of the air under analysis, on two counts. First, the particles have sizes extending over a large range, whereas those of most concern are the small particles--less than 2 μm in diameter. These can enter the lung and produce serious damage, whereas most larger particles are removed by the upper respiratory passages and, although they may be irritating and uncomfortable, are not known to cause serious health effects in most people. Second, total sulfate does not accurately reflect the health aspect of polluted air, because the effects of the fine-particle fraction depend strongly on acidity. Sulfate in the form of sulfuric acid is severely toxic; sulfate of the nonacid type contributes much less to the damage caused by fine particles. Bisulfates (acid sulfate salts) that can be present in the fine-particle fraction appear to be intermediate in effect.

It is apparent, then, that an analysis of particles in air that is to give reliable information on the possible health effects of breathing such air must be able to differentiate the fine- and coarse-particle fractions and must yield information on the kinds and relative amounts of chemical species in the fine fraction. Methods for such analyses are much more complicated than the relatively simple analyses for sulfur dioxide and total particles.

Of the two problems--particle-size distribution and chemical analysis of particles--the former is the simpler. By the use of several devices, such as impactors and diffusion batteries, it is feasible to separate fractions that have defined particle-size ranges. Particles associated with fossil-fuel combustion often have a distinctly bimodal size distribution. The larger particles are probably produced by dispersion of material originally in more massive form, such as fly ash and soot particles, and the smaller particles by condensation and accumulation of substances originally gaseous or very finely subdivided. These fine particles have a limited growth; the minimum in size distribution is in the range of 2-3 μm.

Because of this bimodal distribution of particles in air, it is considered most practical to limit fractionation to two fractions, divided at about 2 μm. This has given rise to the "dichotomous filter" now coming into wide use. It is not yet known whether such measurement of the amounts of coarse and fine fractions correlates with the health effects of air samples. Furthermore, if health damage does depend on the amount of fine particles, is one "small size" fraction adequate or is further fractionation necessary?

Analysis for acidity is exacting. Because very small amounts of acid material in the sample may have health significance, the test must be very sensitive and is therefore all the more subject to interfering substances. Nonetheless, these analyses can be done routinely at a present cost about 3 times that of a test for total water-soluble sulfates. Much remains to be done to relate such analyses to health damage in animals and man.

Fossil fuels contain a vast number of different elements. We have so far dealt largely with only one: sulfur. Many of the other elements are toxic in elemental or salt form. Many are easily detectable in the effluent from fossil-fuel combustion. Some are in the coarse fraction and some, which are volatile, are principally in the aerosols--the fine particle fraction. Analysis for these substances in the minute quantities that are present in ambient air is very difficult and can be done only in a specialized laboratory. Significant advances have been made recently in applying x-ray fluorescence spectroscopy to the problem. As many as 35 elements have been quantitatively analyzed in fine-fraction particles from ambient air. Only fragmentary information is available on the toxicity of these materials in the concentrations found in air.

Besides their possible direct effects on human health, many of these trace elements catalyze transformation of combustion products into other compounds; e.g., the ratio of sulfate to sulfur dioxide in the surrounding air is greater when a high-sulfur oil containing relatively large amounts of vanadium is burned than when an oil containing less vanadium is burned. Vanadium oxides are well-known catalysts for conversion of sulfur dioxide to the sulfur(VI) state. It is now recognized that such transformations of combustion products occur during the dispersion of the products over wide areas--as far as 1,500 km from the source.

Nitrogen oxides are generally considered to be much less important than sulfur oxides in the emission from coal and oil combustion in power plants. Important concentrations of nitrogen oxides are found in areas of dense automobile traffic. Although nitrogen oxides have been largely ignored in rural areas, they may be an important health hazard in urban areas.

PERSONAL MONITORS OF POLLUTION

One of the more effective methods of assessing air pollutants that produce adverse health effects is the intensive study of a group of people over a period during which the extent of pollution varies. Such studies, using diaries or physiologic measurements to record responses, have elicited information that has been used in dose-response formulations aimed at establishing air-quality standards for protection of the general populations.

Unfortunately, the careful measurement of response in these studies has not been matched by equally careful attention to dose. Most often, the dose part of the dose-response curve has been obtained from a fixed monitoring station that is used to typify the exposure of a relatively large area. Various microenvironmental conditions will greatly modify the degree of pollutant exposure for any person within the area. Large differences between indoor and outdoor pollution have been noted in several studies. Furthermore, it has recently been demonstrated that gas appliances, including kitchen stoves, can produce indoor concentrations of nitrogen dioxide that exceed the current air-quality standards.[81]

Other factors that can modify individual dose include the locations of trees and shrubbery, the type of indoor ventilation, and even such mundane matters as the presence of wall and floor coverings. Although indoor air-pollutant concentrations are generally lower than those outdoors, the difference depends on the pollutant.

To minimize these confounding variables in measuring dose, it would be extremely useful to develop personal pollution monitors that accurately measure the dose to individual participants of epidemiologic studies. There have been some recent advances in this direction, including the use of transistorized miniature devices, often with telemetry. However, these are still somewhat cumbersome and relatively expensive for any large-scale study. Among other devices is one developed by Palmes and colleagues that is inexpensive, lightweight, pen-sized, and readily adaptable for use in the measurement of personal pollutant exposure.[98,99] is a cylinder at the bottom of which are wire-mesh screens that contain an absorbent and a reactant for the gas to be measured. Removal of the upper cap allows diffusion of the gas through the orifice to the mesh screens. When reagent is added directly to the cylinder, the amount of gas reacting with the appropriate absorbent can be measured spectrophotometrically. Outside gas concentrations are calculated on the basis of simple diffusion principles, inasmuch as the gas concentration at the bottom of the cylinder is zero. This ingenious device can provide only time-weighted averages, thereby missing peak pollutant concentrations of possible importance; and a suitable absorbent is needed for each pollutant of interest. Thus far, it has been demonstrated to be accurate for the measurement of sulfur dioxide and nitrogen dioxide.

Other personal pollution monitors have been devised, including a Bureau of Mines cyclone for respirable particles,[113] and some techniques have been described in recent workshop reports.[82,134] The development of a variety of techniques should be encouraged for some pollutants (e.g., ozone) that require an emphasis on measuring short-term peaks, rather than on integrating total exposure.

Widespread application of passive monitors in epidemiologic studies is possible and needed now. Development of more versatile devices is also needed. Personal exposure monitoring is the only way to measure short-time exposures; passive monitors cannot do this job. Most of the research effort in developing devices for personal monitoring should be directed to method of measurement--be it electrochemical, solid-state electronic, chemiluminescent, or other--and to the method of handling and preparing the sample. Data can be gathered for short averaging periods by storing separate samples in the device (as on gel tape) for later analysis or by using a "real-time" analytic device and taking advantage of miniaturized solid-state electronics for data storage. Some effort has been devoted to devices that report exposure measurements continually by radio to a control station. Analysis of data takes months or years, so instant reporting of data offers no advantage for epidemiologic studies. Automatic reporting may avoid the need to call on participants individually to collect results, but, in such a study, it probably will be necessary to call on each participant frequently for other reasons, anyway. Automatic telemetric or radio reporting of exposure data is not a priority research subject.

RESEARCH PRIORITIES

- Improved methods for analyzing particle size distribution are needed.

- Improved methods for analysis of the chemical species in fine aerosols should be developed.

- Concentrations of toxic metals in the combustion effluent and in the fine and aerosol fractions should be investigated.

- These analyses should be correlated with concentrations that damage health. Only fragmentary information is available on the degree of accuracy required in analysis of pollutants in air, if air quality is to be gauged on the basis of analytic results.

- Personal monitors that are adequate for subtler analyses now thought necessary must be developed.

V

MUTAGENESIS BY FOSSIL-FUEL COMBUSTION PRODUCTS

There is epidemiologic and toxicologic evidence that airborne fossil-fuel combustion products are mutagenic. The mutagenic effect of primary concern related to these pollutants is carcinogenesis. At the outset, two points should be stressed:

- More data are needed from a combination of epidemiologic and experimental approaches before it can be stated with confidence that specific concentrations of specific products of fossil-fuel combustion pose a significant carcinogenic threat to exposed segments of the population.

- Available data suggest that the major health effects of these pollutants are acute and chronic respiratory dysfunction and secondary heart failure.

Most of the epidemiologic evidence of a mutagenic effect of fossil-fuel combustion products consists of studies documenting a higher incidence of lung cancer in urban areas than in rural areas. Interpretation of any one of these studies is difficult, because of likely confounding variables, the major ones being cigarette-smoking and occupation. However, a higher incidence of lung cancer in urban areas than in rural areas, not apparently explainable by these other factors, has been a reasonably consistent finding in studies performed around the world.

It has been assumed *a priori* that a likely candidate for the causative urban factor in lung cancer is air pollution, inasmuch as the lung is at first-line risk from inhaled agents. However, other factors perhaps related to urban life cannot be completely ruled out. As discussed below, there is ample toxicologic evidence from *in vitro* and animal studies that one or more air pollutants could cause urban lung cancer, but there is not direct definitive evidence linking inhalation of air pollutants at ambient concentrations to lung cancer in animals.

For the purposes of presentation, the toxicologic evidence bearing on mutagenicity is described here by individual air pollutant. But it must be emphasized that urban air contains a complex mixture of pollutants, whose components may be acting in a combined fashion to produce lung cancer.

SULFUR DIOXIDE

In vitro biochemical studies have demonstrated that sulfur dioxide is capable of altering DNA by deaminating cytosine. Theoretically, this could be mutagenic. However, because the optimal pH of this reaction is well below the physiologic range, it is questionable whether it would occur *in vivo*. Sulfite and bisulfite ions may also be involved in free-radical reactions of potential mutagenic importance, but again there is no evidence of such an effect *in vivo*. Evidence of bisulfate mutagenesis has been observed in bacteria and in bacteriophage. However, mutagenesis was observed at low pH, and not at physiologic pH. Chromosomal abnormalities have also been noted in tissue culture and in pollen after exposure to sulfur dioxide. The subject of sulfur oxide mutagenesis has recently been reviewed by Fishbein[40] and by Shapiro.[110]

One study of an increased lung-tumor incidence in animals chronically exposed to sulfur dioxide has been reported; however, the sulfur dioxide concentration was 500 ppm.[100] Perhaps more pertinent is a study demonstrating that inhalation of sulfur dioxide at 3.5 ppm with benzopyrene results in a higher incidence of lung cancer in animals than does inhalation of benzopyrene alone.[71] Of interest is the epidemiologic observation in smelter workers that the association of respiratory cancer with arsenic exposure is increased by concomitant sulfur dioxide exposure.[74]

PHOTOCHEMICAL OXIDANTS

In comparison with the literature on other criteria-document air pollutants, there is a reasonably extensive literature on the mutagenicity of ozone. The available information presents an intriguing paradox. On the one hand, evidence from animal and *in vitro* studies that ozone is mutagenic is sufficiently strong that, if ozone were simply a food additive, it would be banned. On the other hand, despite about three decades of substantial exposure to photochemical air pollution, epidemiologic evidence of increased lung cancer in southern California is lacking. Indications that ozone or its products are potential mutagens include the demonstration of alteration of nucleic acid constituents, chromosomal abnormalities in tissue-culture systems, mutagenicity in bacteria, reported increases in pulmonary neoplasia in both high-tumor-incidence and low-tumor-incidence animal strains, positive and negative studies in humans and animals of chromosomal abnormalities in peripheral-blood lymphocytes after inhalation at ambient concentrations, and a report of teratogenesis and increased fetal wastage in mice.[50,90]

Further epidemiologic study of a possible mutagenic effect of ozone is badly needed. Southern California has large numbers of recent immigrants and a relatively mobile population. More information is also needed about interactions between ozone and aromatic carcinogens. Ozone has been reported to activate such compounds directly to proximal bacterial mutagens in the absence of hepatic microsomes and, on further exposure, to destroy their mutagenicity. In this regard, studies have demonstrated that ozone inhalation produces a decrease in lung benzopyrene hydroxylase activity and cytochrome P-450. These findings might argue that ozone could either potentiate lung carcinogenesis due to aromatic hydrocarbons or protect against this process. Obviously, further information about the interaction of ozone with aromatic hydrocarbon carcinogens is necessary, especially information based on long-term combined-exposure animal studies. Another subject for possible study, if ozone exposure is confirmed to produce lymphocyte chromosomal abnormalities, is the pathway responsible for this finding, inasmuch as it is highly unlikely that reacted ozone could reach the nucleus of circulating lymphocytes. Studies of the mutagenicity of other photochemical oxidants are required.

NITROGEN OXIDES

The major nitrogen oxides formed in fossil-fuel combustion are nitric oxide and nitrogen dioxide. Neither has been clearly implicated in mutagenesis. There is, however, some evidence that these primary oxides of nitrogen may be converted by atmospheric chemical reactions to other, potentially mutagenic agents. In particular, nitrous acid has been shown to be mutagenic in a number of systems. DNA damage apparently occurs through the deamination of guanine, adenine, and cytosine. Cross-linking of DNA by nitrous acid has also been suggested.[40]

A second potential mutagenic hazard imputed to atmospheric oxides of nitrogen is the formation of nitrosamines, many of which have been demonstrated to be carcinogenic in laboratory animals. They are readily formed by the reaction of nitrate with widely available amine compounds. The extent to which atmospheric oxides of nitrogen eventually participate in the formation of *N*-nitroso carcinogens and the impact of these derivatives on human cancer incidence remain conjectural.

POLYCYCLIC ORGANIC MATTER

The carcinogenecity and mutagenicity of polycyclic organic matter (POM), the concentrations of POM in the atmosphere, and the contributions of fossil-fuel combustion have all been well assessed.[85,122,136] The main sources of atmospheric POM are related to fossil fuels. These include coal-refuse burning, hand-stoked

coal furnaces, coking, gasoline-powered automobile and truck engines, and rubber-tire wear. Intermediate-size coal furnaces, petroleum-cracking, and residual oil and gas furnaces are lesser sources. Large coal- and oil-fired power plants are much smaller contributors. Although the big sources (coal-refuse burning and small coal furnaces) have been decreasing, coal conversion (gasification and liquefaction) could become important. As a sidelight, wood combustion is an increasing source of POM, already of about the same magnitude as automobiles.

There are many important POM compounds. Most studies have used benzene-soluble fractions or benzo[a]pyrene as an index. Further work is needed to explore the suitability of these and other indexes for their representativeness of the carcinogenicity of such compounds in fossil fuels, their effluents, and ambient air.

Epidemiologic studies have tentatively associated urban lung-cancer incidence with benzopyrene. Tumor production observed in animals treated with organic extracts of collected airborne particles has been ascribed to POM, although other mutagens are also reported to be present in both organic and inorganic fractions of airborne particles. Much more information is needed on the organic chemical constituents of respirable particles. Also of potential importance are the possible interactions between airborne organic compounds and other atmospheric pollutants, including ozone, nitrogen oxides, and sulfur dioxide.

TRACE ELEMENTS

Potentially mutagenic trace elements are emitted during combustion of fossil fuels. These include arsenic, chromium, cadmium, and various radionuclides. Little is known about how these agents contribute to environmental mutagenesis or about the relative contribution of fossil-fuel combustion to body burden.

Some information on arsenic warrants emphasis. Epidemiologic evidence demonstrating an asssociation of cancer incidence with arsenic in the work environment or in drinking water has recently been supported by basic research documenting that arsenite inhibits DNA repair. And an epidemiologic survey of smelter workers suggested a synergistic interaction between arsenic and sulfur dioxide in association with lung cancer. Increased use of coals that are relatively high in arsenic content will presumably increase anthropogenic atmospheric arsenic.

RECOMMENDATIONS FOR RESEARCH

- Further epidemiologic study is necessary to determine whether the urban factor associated with lung cancer is, in fact,

contributed by air pollution. In general, such studies should be limited to groups in which previous data suggested that a relatively large effect is likely to be demonstrable and in which cigarette-smoking and occupation can be rigorously controlled. Whenever possible, information concerning dose should be obtained, to characterize the responsible pollutants. Carcinogenicity potentially due to photochemical oxidants is a special situation that requires careful study of the southern California population.

- Additional experimental studies on animals and tissue-culture systems are necessary, to test hypotheses resulting from epidemiologic work and to provide direction for more focused studies on human populations. Carcinogenesis studies in animals should ask carefully defined questions relevant to human exposure, with emphasis on mechanisms of oncogenesis (e.g., transport and metabolism of specific pollutants and cocarcinogenic effects). A valid animal model of human lung cancer would greatly aid such investigations.

- Considerable further work with *in vitro* systems should be encouraged as a rapid and inexpensive way of obtaining leads to be explored in animals and human populations. In addition to testing of the Ames type, *in vitro* screening approaches involving measurements of effects on DNA repair enzymes, on chromosomal breakage, and on cell transformation should be used to provide preliminary evidence of carcinogenic and mutagenic potential in products of fossil-fuel combustion.

- It is possible that mutagenic effects of fossil-fuel combustion products result from interactions between pollutants, rather than from one pollutant acting alone. Further information should be obtained on such potential interactions at levels ranging from the subcellular to the macroenvironmental.

REFERENCES

1. Alarie, Y., C. E. Ulrich, W. M. Busey, H. E. Swann, Jr., and H. N. MacFarland. Long-term continuous exposure of guinea pigs to sulfur dioxide. Arch. Environ. Health 21:769-777, 1970.

2. Amdur, M. O. Respiratory absorption data and SO_2 dose-response curves. Arch. Environ. Health 12:729-732, 1966.

3. Amdur, M. O. Toxicological guidelines for research on sulfur oxides and particulates, pp. 48-55. In Proceedings of the Fourth Symposium on Statistics and the Environment. March 3-5, 1976, Washington, D.C. Sponsored by the American Statistical Association, American Society for Quality Control, Committee on National Statistics, and Committee on Toxicology of the National Academy of Sciences-National Research Council. Washington, D.C.: American Statistical Association, 1977.

4. American Meteorological Society, 1977 Committee on Atmospheric Turbulence and Diffusion. Accuracy of dispersion models. Bull. Amer. Meteor. Soc. 59:1025-1026, 1978.

5. Antizzo, J., Ed. Background Material for Workshop on Health and Environmental Effects of Coal Gasification and Liquefaction Technologies. Report M78-58. McLean, Va.: Mitre Corp., 1978. 265 pp.

6. Babu, S. P. Trace Elements in Fuel. Washington, D.C.: American Chemical Society, 1975. 216 pp.

7. Bell, K. A., W. S. Linn, M. Hazucha, J. D. Hackney, and D. V. Bates. Respiratory effects of exposure to ozone plus sulfur dioxide in southern Californians and eastern Canadians. Amer. Ind. Hyg. Assoc. J. 38:696-706, 1977.

8. Bencko, V., and K. Symon. Health aspects of burning coal with a high arsenic content. I. Arsenic in hair, urine, and blood in children residing in a polluted area. Environ. Res. 13:378-385, 1977.

9. Bencko, V., K. Symon, V. Chladek, and J. Pihrt. Health Aspects of burning coal with a high arsenic content. II. Hearing changes in exposed children. Environ. Res. 13:386-395, 1977.

10. Billings, C. E., A. M. Sacco, W. R. Matson, R. M. Griffin, W. R. Coniglio, and R. A. Harley. Mercury balance on a large pulverized coal-fired furnace. J. Air Pollut. Control Assoc. 23:773-777, 1973.

11. Biological Implications of Metals in the Environment. Proceedings of the 15th Annual Hanford Life Sciences Symposium at Richland, Wash., 1975. ERDA Symposium Series, CONF-750929/RAS, 1977. 9.

12. Blake, K. C. H. Absorption of 203 Pb from gastrointestinal tract of man. Environ. Res. 11:1-4, 1976.

13. Plock, C., and R. Dams. Study of fly ash emission during combustion of coal. Environ. Sci. Technol. 10:1011-1017, 1976.

14. Boatman, E. S., S. Sato, and R. Frank. Acute effects of ozone on cat lungs. II. Structural. Amer. Rev. Resp. Dis. 110:157-169, 1974.

15. Bolton, N. E., R. I. Van Hook, W. Fulkerson, J. F. Emery, W. S. Lyon, A. W. Andren, and J. A. Carter. Trace Element Measurements at the Coal-Fired Allen Steam Plant. Progress Rept. February 1973-July 1973. ORNL-NSF-EP-62. Oak Ridge, Tenn.: Oak Ridge National Laboratory, 1974. 47 pp.

16. Bolton, N. E., R. I. Van Hook, W. Fulkerson, W. S. Lyon, A. W. Andren, J. A. Carter, and J. F. Emery. Trace Element Measurements at the Coal-Fired Allen Steam Plant. Progress Report June 1971-January 1973. ORNL-NSF-EP-43. Oak Ridge, Tenn.: Oak Ridge National Laboratory, 1973. 83 pp.

17. Booth, R. S., and S. V. Kaye. A Preliminary System Analysis Model of Radioactivity Transfer to Man from Deposition in a Terrestrial Environment. ORNL-TM-3135. Oak Ridge, Tenn.: Oak Ridge National Laboratory, 1971. 21 pp.

18. Bowman, R. D., Jr., and D. Sanderson. Temperature Related Deficiencies and the Federal Reference Method for Ambient SO_2 Measurement. Presented at the Annual Conference of the Florida Section of the Air Pollution Control Association, Sept. 27-28, 1976, Cape Coral, Florida. 22 pp.

19. Brainstein, H. M., E. D. Copenhaver, and H. A. Pfuderer, Eds. Oak Ridge National Laboratory. Environmental, Health and Control Aspect of Coal Conversion. An Information Overview. Vols. 1 and 2. ORNL/E 1595. Oak Ridge, Tenn.: Oak Ridge National Laboratory, 1977. 79 pp.

20. Buechley, R. W., W. B. Riggan, V. Hasselblad, and J. B. VanBruggen. SO_2 levels and perturbations in mortality. A study in the New York-New Jersey metropolis. Arch. Environ. Health 27:134-137, 1973.

21. Chamberlain, A. C., W. S. Clough, M. J. Heard, D. Newton, A. N. B. Scott, and A. C. Wells. Uptake of lead by inhalation of motor exhaust. Proc. R. Soc. Lond. B 192:77-110, 1975.

22. Cherian, M. G., J. B. Hursh, T. W. Clarkson, and J. Allen. Radioactive mercury distribution in biological fluids and excretion in human subjects after inhalation of mercury vapor. Arch. Environ. Health 33:109-114, 1978.

23. Ciocco, A., and D. J. Thompson. A follow-up of Donora ten years after. Methodology and findings. Amer. J. Public Health 51:155-164, 1961.

24. Clarkson, T. W. Epidemiological and experimental aspects of lead and mercury contamination of food. Food Cosmet. Toxicol. 9:229-243, 1971.

25. Coles, D. G., R. C. Ragaini, and J. M. Ondov. Behavior of natural radionuclides in western coal-fired power plants. Environ. Sci. Technol. 12:442-446, 1978.

26. Comar, C. L., and N. Nelson. Health effects of fossil fuel combustion products. Report of a workshop. Environ. Health Perspect. 12:149-170, 1975.

27. Council on Environmental Quality. Environment and Conservation in Energy Research and Development. Assessing the Adequacy of Federal Programs. A Report under Section 11 of the Nonnuclear Energy Research and Development Act (P.L. 93-577). Washington, D.C.: U.S. Government Printing Office, 1976. 117 pp.

28. Curry, J. J. The action of histamine on the respiratory tract in normal and asthmatic subjects. J. Clin. Invest. 25:785-791, 1946.

29. Davidson, C. I. The deposition of trace metal-containing particles in the Los Angeles area. Powder Technol. 18:117-126, 1977.

30. de Bruin, A. Biochemical Toxicology of Environmental Agents. Amsterdam: Elsevier-North Holland Biomedical Press, 1976. 1544 pp.

31. Dietz, R. N., R. F. Wieser, and L. Newman. An Evaluation of the Modified EPA Method 6 Flue Gas Sampling Procedure. Presented at the Workshop on Measurement Technology and Characterization of Primary Sulfur Oxides Emission from Combustion Sources, Southern Pines, N.C., April 24-26, 1978. BNL #24367. Upton, N.Y.: Brookhaven National Laboratory, 1978. 28 pp.

32. Dietz, R. N., R. F. Wieser, and L. Newman. Operating Parameters Affecting Sulfate Emissions from an Oil-Fired Power Unit. Presented at the Workshop on Measurement Technology and Characterization of Primary Sulfur Oxides Emission from Combustion Sources, Southern Pines, N.C., April 24-26, 1978. Upton, N.Y.: Brookhaven National Laboratory, 1978. 32 pp.

33. Dreesen, D. R., E. S. Gladney, J. W. Owen, B. L. Perkins, C. L. Wienke, and L. E. Wangen. Comparison of levels of trace elements extracted from fly ash and levels found in effluent waters from a coal-fired power plant. Environ. Sci. Technol. 11:1017-1019, 1977.

34. du Pont, E. I., de Nemours and Co., Savannah River Laboratory. Annual Report. 1976. Savannah River Laboratory Environmental Transport and Effects Research. DP 1455. Aiken, S.C.: E. I. du Pont de Nemours and Co., 1977.

35. Eisenberg, L. The social imperative of medical research. Science 198:1105-1110, 1977.

36. Ellison, J. McK., and R. E. Waller. A review of sulphur oxides and particulate matter as air pollutants with particular reference to effects on health in the United Kingdom. Environ. Res. 16:302-325, 1978.

37. Empey, D. W., L. A. Laitinen, L. Jacobs, W. M. Gold, and J. A. Nadel. Mechanisms of bronchial hyperreactivity in normal subjects after upper respiratory tract infection. Amer. Rev. Resp. Dis. 113:131-139, 1976.

38. Ferris, B. G., Jr. Epidemiology standardization project. Amer. Rev. Resp. Dis. 118(6,Pt.2):1-120, 1978.

39. Ferris, B. G., Jr. Health effects of exposure to low levels of regulated air pollutants. A critical review. J. Air Pollut. Control Assoc. 28:482-497, 1978.

40. Fishbein, L. Atmospheric mutagens. I. Sulfur oxides and nitrogen oxides. Mutation Res. 32:309-330, 1976.

41. French, J., et al. Preliminary Assessment of the Current Data on the Public Health Impact Resulting from the Conversion from Oil or Gas to Coal Fuels in Large Utility Boilers. Research Triangle Park, N.C.: U.S. Environmental Protection Agency, National Environmental Research Center, July 1975.

42. Friberg, L., T. Kjellström, G. Nordberg, and M. Piscator. The Karolinska Institute, Stockholm, Sweden. Cadmium in the Environment. III. A Toxicological and Epidemiological Appraisal. Prepared for the U.S. Environmental Protection Agency, Office of Research and Development, Washington, D.C. Publ. No. EPA-650/2-75-049. Springfield, Va.: National Technical Information Service, 1975. 218 pp.

43. Friberg, L., M. Piscator, G. F. Nordberg, and T. Kjellström. Cadmium in the Environment. 2nd ed. Cleveland, Ohio: CRC Press, Inc., 1974. 248 pp.

44. Friberg, L. T., and J. J. Vostal. Mercury in the Environment. Cleveland, Ohio: Chemical Rubber Company, 1972. 232 pp.

45. Gaarenstroom, P. D., S. P. Perone, and J. L. Moyers. Application of pattern recognition and factor analysis for characterization of atmospheric particulate composition in southwest desert atmosphere. Environ. Sci. Technol. 11:795-800, 1977.

46. Gillespie, J. R., D. Hyde, D. Dungworth, and J. Stara. Functional and Structural Studies on the Lungs of Beagles Exposed for 5 Years to High Ambient Levels of Auto Exhaust and Other Air Pollutants. Presented at 27th International Congress of Physiological Sciences, Paris, France, 1977.

47. Gilsinn, J. F. Estimates of the Nature and Extent of Lead Paint Poisoning in the United States. U.S. Department of Commerce, National Bureau of Standards Technical Note 746. Washington, D.C.: U.S. Government Printing Office, 1972. 151 pp.

48. Glass, G. E. Identification and distribution of inorganic components in water. What to measure? Ann. N.Y. Acad. Sci. 298:31-46, 1977.

49. Golden, J. A., J. A. Nadel, and H. A. Boushey. Bronchial hyperirritability in healthy subjects after exposure to ozone. Amer. Rev. Resp. Dis. 118:287-294, 1978.

50. Goldstein, B. D. Cellular effects of ozone. Rev. Environ. Health 2:177-202, 1977.

51. Gordon, G. E., W. H. Zoller, and E. S. Gladney. Abnormally enriched trace elements in the atmosphere, pp. 167-173. In D. C. Hemphill, Ed. Trace Substances in Environmental Health. VII. Proceedings of University of Missouri's 7th Annual Conference on Trace Substances in Environmental Health. Held at Memorial Union, University of Missouri-Columbia, Columbia, Missouri, June 12, 13, and 14, 1973. Columbia, Mo.: University of Missouri, 1973. 460 pp.

52. Goyer, R. A., and M. A. Mehlman, Eds. Toxicology of Trace Elements. Advances in Modern Toxicology. Vol. 2. New York: John Wiley and Sons Co., 1977. 303 pp.

53. Great Britain, Ministry of Health. Mortality and Morbidity during the London Fog of December 1952. Reports on Public Health and Medical Subjects No. 95. London: Her Majesty's Stationery Office, 1954. 61 pp.

54. Hanna, S. R., G. A. Briggs, J. Deardorff, B. A. Egan, F. A. Gifford, and F. Pasquill. AMS Workshop on Stability Classification Schemes and Sigma Curves. Summary of recommendations. Bull. Amer. Meteor. Soc. 58:1305-1309, 1977.

55. Hers, J. F., and J. Mulder. Broad aspects of the pathology and pathogenesis of human influenza. Amer. Rev. Resp. Dis. 83(2,Pt.2):84-97, 1961.

56. Holtzman, M., J. Sheller, J. Cunningham, G. Irsigler, J. Nadel, and H. Boushey. Effect of ozone on bronchial reactivity in atopic and non-atopic subjects. Amer. Rev. Resp. Dis. 119(Suppl.):71, 1979. (abstract)

57. Hopps, H. C., and H. L. Cannon, Eds. Geochemical environment in relation to health and disease. Ann. N.Y. Acad. Sci. 199:1-352, 1972.

58. Horton, J. H., R. S. Dorsett, and R. E. Cooper. Trace Elements in the Terrestrial Environment of a Coal-Fired Powerhouse. Savannah River Laboratory. DP-1475. Aiken, S.C.: du Pont de Nemours and Co., 1977.

59. Horton, J. H., and J. W. McMinn. Ash Basin Reclamation with Forest-Trees. Savannah River Laboratory. DP-1477. Aiken, S.C.: E. I. du Pont de Nemours and Co., 1977.

60. Hyde, D., J. R. Gillespie, R. Carter, and J. Orthoefer. Correlations of pulmonary structural and functional changes in dogs after long-term exposure to auto exhausts and other pollutants. Amer. Rev. Resp. Dis. 177:243, 1978.

61. Interagency Working Group on Health and Environmental Effects of Energy Use. Report prepared for the Office of Management and Budget and the Council on Environmental Quality, Nov. 1974.

62. International Commission on Radiological Protection, Committee 2. Report of the Task Group on Reference Man. ICRP Publication 23. Oxford: Pergamon Press, 1975. 480 pp.

63. Iyengar, G. V., W. E. Kollmer, and H. J. M. Bowen. The Elemental Composition of Human Tissues and Body Fluids. A Compilation of Values for Adults. New York: Verlag Chemie, 1978. 151 pp.

64. Jacko, R. B., and D. W. Neuendorf. Trace metal particulate emission test results from a number of industrial and municipal point sources. J. Air Pollut. Control Assoc. 27:989-994, 1977.

65. Jones, R. N., and H. Weill. Occupational lung disease. Basis of RD 6(3):1-6, 1978.

66. Kaakinen, J. W., and R. M. Jorden. Determination of a trace element mass balance for a coal-fired power plant, pp. 165-184. In W. Fulkerson, W. D. Schults, and R. I. Van Hook, Eds. Proceedings of the First Annual NSF Trace Contaminants Conference held in Oak Ridge, Tenn., 8 Aug. 1973. Oak Ridge National Laboratory Report CONF 730802. Springfield, Va.: National Technical Information Service, 1974.

67. Kalb, G. W. Total mercury mass balance at a coal-fired power plant, pp. 154-174. In S. P. Babu, Ed. Trace Elements in Fuel. Advances in Chemistry Series No. 141. Washington, D.C.: American Chemical Society, 1975.

68. Kessler, G.-F., J. H. M. Austin, P. D. Graf, G. Gamsu, and W. M. Gold. Airway constriction in experimental asthma in dogs. Tantalum bronchographic studies. J. Appl. Physiol. 35:703-708, 1973.

69. Klein, D. H., A. W. Andren, J. A. Carter, J. F. Emery, C. Feldman, W. Fulkerson, W. S. Lyon, J. C. Ogle, Y. Talmi, R. I. Van Hook, and N. Bolton. Pathways of thirty-seven trace elements through coal-fired power plant. Environ. Sci. Technol. 9:973-979, 1975.

70. Lambert, H. P., and H. Stern. Infective factors in exacerbations of bronchitis and asthma. Brit. Med. J. 3:323-327, 1972.

71. Laskin, S., M. Kuschner, and R. T. Drew. Studies in pulmonary carcinogenesis, pp. 321-350. In M. G. Hanna, Jr., P. Nettesheim, and J. R. Gilbert, Eds. Inhalation Carcinogenesis. Proceedings of a Biology Division, Oak Ridge National Laboratory, Conference held in Gatlinburg, Tenn., Oct. 8-11, 1969. Oak Ridge, Tenn.: U.S. Atomic Energy Commission, 1970.

72. Lave, L. B., and E. P. Seskin. Air Pollution and Human Health. Publication for Resources for the Future. Baltimore, Md.: Johns Hopkins Univ. Press, 1978. 368 pp.

73. Lawther, P. J., R. E. Waller, and M. Henderson. Air pollution and exacerbations of bronchitis. Thorax 25:525-539, 1970.

74. Lee, A. M., and J. F. Fraumeni, Jr. Arsenic and respiratory cancer in man. An occupational study. J. Natl. Cancer Inst. 42:1045-1052, 1969.

75. Lee, L.-Y., E. R. Bleecker, and J. A. Nadel. Effect of ozone on bronchomotor response to inhaled histamine aerosol in dogs. J. Appl. Physiol. 43:626-631, 1977.

76. Lenihan, J., and W. W. Fletcher, Eds. The Chemical Environment. Environment and Man. Vol. 6. New York: Academic Press, 1977. 163 pp.

77. Logan, W. P. D. Mortality in London fog incident. Lancet 1:336-338, 1953.

78. McBride, J. P., R. E. Moore, J. P. Witherspoon, and R. E. Blanco. Radiological impact of airborne effluents of coal and nuclear plants. Science 202:1045-1050, 1978.

79. McLellan, J. S., P. R. Flanagan, M. J. Chamberlain, and L. S. Valberg. Measurement of dietary cadmium absorption in humans. J. Tox. Environ. Health 4:131-158, 1978.

80. McMullen, T. B., and R. B. Faoro. Occurrence of eleven metals in airborne particulates and in surficial materials. J. Air Pollut. Control Assoc. 27:1198-1202, 1977.

81. Melia, R. J. W., C. du V. Florey, S. C. Darby, E. D. Palmes, and B. D. Goldstein. Differences in NO_2 levels in kitchens with gas or electric cookers. Atmos. Environ. 12:1379-1381, 1978.

82. Morgan, M. G., and S. C. Morris. Individual Air Pollution Monitors. An Assessment of National Research Needs. Report of a workshop held at Brookhaven National Laboratory, Upton, N.Y., July 8-10, 1975. BNL Publ. No. 50482. Springfield, Va.: National Technical Information Service, 1976. 31 pp.

83. Nadel, J. A., H. Salem, B. Tamplin, and Y. Tokiwa. Mechanisms of bronchoconstriction during inhalation of sulfur dioxide. J. Appl. Physiol. 20:164-167, 1965.

84. National Research Council, Committee on Biologic Effects of Atmospheric Pollutants. Lead. Airborne Lead in Perspective. Washington, D.C.: National Academy of Sciences, 1972. 330 pp.

85. National Research Council, Committee on Biologic Effects of Atmospheric Pollutants. Particulate Polycyclic Organic Matter. Washington, D.C.: National Academy of Sciences, 1972. 361 pp.

86. National Research Council, Committee on Medical and Biologic Effects of Environmental Pollutants. Airborne Particles. Baltimore, Md.: University Park Press, 1979. 343 pp.

87. National Research Council, Committee on Medical and Biologic Effects of Environmental Pollutants. Arsenic. Washington, D.C.: National Academy of Sciences, 1977. 332 pp.

88. National Research Council, Committee on Medical and Biologic Effects of Environmental Pollutants. Carbon Monoxide. Washington, D.C.: National Academy of Sciences, 1977. 239 pp.

89. National Research Council, Committee on Medical and Biologic Effects of Environmental Pollutants. Nitrogen Oxides. Washington, D.C.: National Academy of Sciences, 1977. 333 pp.

90. National Research Council, Committee on Medical and Biologic Effects of Environmental Pollutants. Ozone and Other Photochemical oxidants. Washington, D.C.: National Academy of Sciences, 1977. 719 pp.

91. National Research Council, Committee on Sulfur Oxides. Sulfur Oxides. Washington, D.C.: National Academy of Sciences, 1978. 209 pp.

92. National Research Council, Environmental Studies Board, Coordinating Committee for Scientific and Technical Assessments of Environmental Pollutants. An Assessment of Mercury in the Environment. Washington, D.C.: National Academy of Sciences, 1977. 183 pp.

93. Nordberg, G. F., Ed. Effects and Dose-Response Relationships of Toxic Metals. Proceedings from an International Meeting Organized by the Subcommittee on the Toxicology of Metals of the Permanent Commission and International Association on Occupational Health, Tokyo, Nov. 18-23, 1974. New York: Elsevier Scientific Publishing Co., 1976. 559 pp.

94. Nriagu, J. O., Ed. The Biogeochemistry of Lead in the Environment. Part B. Biological Effects. Topics in Environmental Health. Vol. 1B. New York: Elsevier-North Holland Biomedical Press, 1978. 397 pp.

95. Oehme, F. W., Ed. Toxicity of Heavy Metals in the Environment. Parts 1 and 2. New York: Marcel Dekker, Inc., 1978, 1979. 515 pp., 970 pp.

96. Ondov, J. M., W. H. Zoller, I. Olmez, N. K. Aras, G. E. Gordon, L. A. Rancitelli, K. H. Abel, R. H. Filby, K. R. Shah, and R. C. Ragaini. Elemental concentrations in the National Bureau of Standards' environmental coal and fly ash standard reference materials. Anal. Chem. 47:1102-1109, 1975.

97. Orehek, J., J. P. Massari, P. Gayrard, C. Grimaud, and J. Charpin. Effect of short-term, low-level nitrogen dioxide exposure on bronchial sensitivity of asthmatic patients. J. Clin. Invest. 57:301-307, 1976.

98. Palmes, E. D., and A. F. Gunnison. Personal monitoring device for gaseous contaminants. Amer. Ind. Hyg. Assoc. J. 34:78-81, 1973.

99. Palmes, E. D., A. F. Gunnison, J. DiMattio, and C. Tomczyk. Personal sampler for nitrogen dioxide. Amer. Ind. Hyg. Assoc. J. 37:570-577, 1976.

100. Peacock, P. R., and J. B. Spence. Incidence of lung tumours in L^x mice exposed to (1) free radicals; (2) SO_2. Brit. J. Cancer 21:606-618, 1967.

101. Pietrzak-Flis, Z., G. L. Rehnberg, M. J. Favor, D. F. Cahill, and J. W. Laskey. Chronic ingestion of cadmium and/or tritium in rats. I. Accumulation and distribution of cadmium in two generations. Environ. Res. 16:9-17, 1978.

102. Pounds, J. G., R. J. Malar, and J. R. Allen. Metabolism of lead-210 in juvenile and adult Rhesus monkeys. Bull. Environ. Contam. Toxicol. 19:684-691, 1978.

103. Prigge, E. Early signs of oral and inhalative cadmium uptake in rats. Arch. Toxicol. 4:231, 1978.

104. Rabinowitz, M., G. Wetherill, and J. Kopple. Delayed appearance of tracer lead in facial hair. Arch. Environ. Health 31:220-223, 1976.

105. Radian Corporation. Environmental Characterization of the CO_2 Acceptor Process. Book 1, Program Summary, 65 pp. Book 2, Data Summary, 178 pp. Book 3, Scale-up Projections, 35 pp. Book 4, Appendices, 428 pp. Austin, Texas: Radian Corporation, 1978.

106. Schimmel, H. Evidence for possible acute health effects of ambient air pollution from time series analysis. Methodological questions and some new results based on New York City. Bull. N.Y. Acad. Med. 54:1052-1108, 1978.

107. Schimmel, H., and L. Greenburg. A study of the relation of pollution to mortality, New York City, 1963-1968. J. Air Pollut. Control Assoc. 22:607-616, 1972.

108. Schimmel, H., and T. J. Murawski. SO_2--harmful pollutant or air quality indicator? J. Air Pollut. Control Assoc. 25:739-740, 1975.

109. Scott, J. A. Fog and deaths in London, December 1952. Public Health Rep. 68:474-479, 1953.

110. Shapiro, R. Genetic effects of bisulfite (sulfur dioxide). Mutation Res. 39:149-176, 1977.

111. Shendrikar, A. D., and G. B. Faudel. Distribution of trace metals during oil shale retorting. Environ. Sci. Technol. 12:332-336, 1978.

112. Simonsson, B. G. Clinical and physiological studies on chronic bronchitis. 3. Bronchial reactivity to inhaled acetylcholine. Acta Allerg. (Kobenhavn) 20:325-348, 1965.

113. Speizer, F. E., Y. Bishop, and B. G. Ferris. An epidemiologic approach to the study of the health effects of air pollution, pp. 56-68. In Proceedings of the Fourth Symposium on Statistics and the Environment. March 3-5, 1976, Washington, D.C. Sponsored by the American Statistical Association, American Society for Quality Control, Committee on National Statistics, and Committee on Toxicology of the National Academy of Sciences-National Research Council. Washington, D.C.: American Statistical Association, 1977.

114. Stevens, R. K., and T. G. Dzubay. Dichotomous Sampler. A Practical Approach to Aerosol Fractionation and Collection. EPA Report 600/2-78-112. Research Triangle Park, N.C.: U.S. Environmental Protection Agency, 1978. 31 pp.

115. Stuik, E. J. Biological response of male and female volunteers to inorganic lead. Int. Arch. Arbeitsmed. 33:83-97, 1974.

116. U.S. Department of Health, Education, and Welfare, Public Health Service, Consumer Protection and Environmental Health Service, National Air Pollution Control Administration. Air Quality Criteria for Particulate Matter. NAPCA Publ. No. AP-49. Washington, D.C.: U.S. Government Printing Office, 1969. 211 pp.

117. U.S. Department of Health, Education, and Welfare, Public Health Service, Environmental Health Service, National Air Pollution Control Administration. Air Quality Criteria for Sulfur Oxides. NAPCA Publ. No. AP-50. Washington, D.C.: U.S. Government Printing Office, 1970. 178 pp.

118. U.S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration, National Institute for Occupational Safety and Health. The Toxicology of Beryllium. PHS Publ. No. 2173. Washington, D.C.: U.S. Government Printing Office, 1972. 50 pp.

119. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Institute of Environmental Health Sciences. Human Health and the Environment. Some Research Needs. Report of the Second Task Force for Research Planning in Environmental Health Sciences. DHEW Publ. No. NIH-77-1277. Washington, D.C.: U.S. Government Printing Office, 1977. 498 pp.

120. U.S. Energy Research and Development Administration. Biological Implications of Metals in the Environment. Proceedings of the Fifteenth Annual Hanford Life Sciences Symposium at Richland, Washington, Sept. 29-Oct. 1, 1975. ERDA Symposium Series 42. CONF-750929. Springfield, Va.: National Technical Information Service, 1977. 682 pp.

121. U.S. Environmental Protection Agency. Health, Environmental Effects, and Control Technology of Energy Use. Proceedings of a National Conference, Feb. 9-11, 1976, Sheraton Park Hotel, Washington, D.C. EPA Report No. 600/7-76-002. Washington, D.C.: Environmental Protection Agency, 1976. 340 pp.

122. U.S. Environmental Protection Agency. Scientific and Technical Assessment Report on Particulate Polycyclic Organic Matter (PPOM). EPA 600/6-75-001. Washington, D.C.: U.S. Environmental Protection Agency, 1975. 94 pp.

123. U.S. Environmental Protection Agency, Air Pollution Control Office. Air Quality Criteria for Nitrogen Oxides. APCO Publ. No. AP-84. Washington, D.C.: U.S. Government Printing Office, 1971. 152 pp.

124. U.S. Environmental Protection Agency, Office of Research and Development. Environmental Research Outlook, FY 1977 through FY 1981. Report to Congress. EPA 600/9-77-002. Washington, D.C.: U.S. Environmental Protection Agency, 1977. 189 pp.

125. University of Maryland. Atmospheric Impact of Major Sources and Consumers of Energy. Progress Report 75. College Park, Md.: University of Maryland, 1975.

126. Van Hook, R. I. Potential Health and Environmental Effects from Trace Elements and Radionuclides from Increased Coal Utilization. Oak Ridge National Laboratory, Report ORNL 5367. Springfield, Va.: National Technical Information Service, 1978. 67 pp.

127. Van Hook, R. I. Transport and transportation pathways of hazardous chemicals from solid waste disposal. Environ. Health Perspect. 27:295-308, 1978.

128. Van Hook, R. I., and W. D. Schults, Eds. Effects of Trace Contaminants from Coal Combustion. Proceedings of a Workshop held in Knoxville, Tenn., Aug. 2-6, 1976. ERDA 77-64. Washington, D.C.: Energy Research and Development Administration, 1977.

129. Vaughan, B. E., K. Abel, D. A. Catalolo, J. M. Hales, C. E. Hane, L. A. Rancitelli, R. C. Routson, R. E. Wildung, and E. G. Wolfe. Review of Potential Impact on Health and Environmental Quality from Metals Entering the Environment as a Result of Coal Utilization. A Battelle Energy Program Report. Richland, Wash.: Battelle Memorial Institute, 1975. 75 pp.

130. von Lehmden, D. J., R. H. Jungers, and R. E. Lee, Jr. Determination of trace elements in coal, fly ash, fuel oil, and gasoline. A preliminary comparison of selected analytical techniques. Anal. Chem. 46:239-245, 1974.

131. Wallace, L. Personal uses in studies of human exposure, pp. 7-19. In Proceedings of the Symposium on the Development and Usage of Personal Monitors for Exposure and Health Effect Studies, held in Research Triangle Park, N.C., June 1979. EPA Report 600/9/79/032. Research Triangle Park, N.C.: U.S. Environmental Protection Agency, Office of Research and Development, Health Effects Research Laboratory, Environmental Systems Laboratory, 1979.

132. Waller, R. E. Air pollution and community health. J. Roy. Coll. Physicians London 5:362-368, 1971.

133. Weil, J. C., and A. F. Jepsen. Evaluation of the Gaussian plume model at the Dickerson Power Plant. Atmos. Environ. 11:901-910, 1977.

134. White, O., Jr., Ed. Proceedings of the Symposium on Assessing the Industrial Hygiene Monitoring Needs for the Coal Conversion and Oil Shale Industries. Brookhaven National Laboratory Publ. No. 51002. Springfield, Va.: National Technical Information Service, 1979. 334 pp.

135. Whittle, K. J., R. Hardy, A. V. Holden, R. Johnston, and R. J. Pentreath. Occurrence and fate of organic and inorganic contaminants in marine animals. Ann. N.Y. Acad. Sci. 298:47-79, 1977.

136. World Health Organization, International Agency for Research on Cancer. Certain Polycyclic Aromatic Hydrocarbons and Heterocyclic Compounds. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 3. IARC Working Group, Lyon, 5-11 Dec. 1972. Geneva: World Health Organization, 1973. 271 pp.